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BLOOD DISORDERS ASSOCIATED WITH PREGNANCY*†

The Value of Sternal Marrow Biopsy

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THE science of hematology has made distinct and rapid progress since the advent of sternal marrow biopsy. The hematologist has been able to study the blood cells in their formative stage. This knowledge has given him a new perspective into the diagnosis and management of the blood dyscrasias.

Pianese[1] (1903) was the first to obtain human bone marrow during life for examination. He punctured the femur of a patient, and obtained bone marrow for study. In this same year, Wolff[2] utilized trepanation of the tibia and femur in experimental animals, and he suggested the clinical use of bone marrow biopsies.

The pioneer of bone marrow biopsy was Ghedini.[3] In 1908, he described a method of trephining the upper end of the tibia and making sections and smears of the curetted marrow from patients with latent malaria and leishmaniasis. He observed that parasites could be demonstrated in the bone marrow when absent in the peripheral blood; observations that have been repeatedly confirmed in recent years.

Seyfarth,[4] in 1923, advocated the use of the sternum. He used a surgical technique, and removed a small piece of bone marrow. His method, somewhat refined, is still advocated by many hematologists.

Arinkin,[5] in 1927, reported a simple painless method by which a small amount of bone marrow fluid was aspirated from the sternum for diagnostic purposes. This introduction of the needle puncture method was the greatest contribution to the simplification of the technique. He punctured the outer lamina of the sternum with a stout spinal needle with a tightly fitting trocar, and aspirated a mixture of blood and bone marrow. He made films of the aspirated material, and studied the stained slides histologically.

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Since then, many experimental and clinical studies of the bone marrow have been made. The findings in both health and disease are well known. Bone marrow biopsy is now a standardized procedure in the study of the blood and its disorders. It is not a "cure all," but is important in the proper evaluation of abnormal blood states. In many cases it is the key to the diagnosis. The study of an abnormal blood picture is not complete without an analysis of the sternal marrow.

Although there are voluminous reports on the findings of the sternal marrow in health and disease, there have been extremely few studies in relation to the blood problems associated with pregnancy.

The myeloid, erythroid, and megakaryocytic groups of cells all originate within the bone marrow. This hemopoietic activity is constantly occurring, throughout life, in the marrow of the ribs, vertebrae, and sternum. The bone marrow of the long bones is relatively inactive, but remains as a reservoir that can become active when necessary. This hemopoietic activity of the sternal marrow is present at birth and sustained throughout life. The sternal marrow has been shown to be indicative of the character of the hemopoietic tissues as a whole.[6]

The two methods of sternal bone marrow biopsy in general use are the trephine and aspiration.

The trephine method is a surgical procedure. Under local anesthesia, a small incision is made into the sternum. A small piece of bone marrow is removed. Paraffin sections are made and stained for examination. Smears or imprints may also be made. While the topographic relationships of the marrow are preserved in sections, smear or imprints are necessary for accurate identification of the various cells seen in normal and pathologic conditions.

Although this biopsy method is preferred by many investigators, its great drawback is that it is a surgical procedure. Despite the anesthetic, it is often painful and cannot readily be repeated on the same patient. Turkel and Bethell[7] have devised a special needle by which a small piece of marrow can be readily curetted and removed through a small puncture wound. This eliminates the "incision hazard" of previous techniques. However, one cannot study the marrow grossly with this method. Another objection is that frequently the tissue removed is too small to be of value.

Sternal aspiration has become the more popular method. The technique is simple, relatively painless, and can be repeated at will on the same patient. The one objection to this method is that along with aspiration of the bone marrow cells, one must of necessity withdraw sinusoidal (or peripheral) blood at the same time. This may dilute the bone marrow so greatly that one can only see a few bone marrow cells on a smear. This one objection has been overcome by the use of the concentration method of Limarzi.[8]

Technique

Limarzi Method.—The second or third interspace is selected for aspiration. Iodine and alcohol are applied to the skin. A small wheal containing 1 per cent procaine is made in the skin over the sternum with a fine hypodermic needle. About two to three cubic

centimeters are injected into the subcutaneous tissue and under the periosteum of the sternum. After anesthesia is obtained, the specially devised sternal needle* is gently but firmly inserted through the anterior wall of the sternum into the bone marrow. A definite "give" is felt as the needle enters the marrow. One cubic centimeter of bone marrow fluid is then aspirated into a dry syringe. This fluid, composed of sinusoidal blood, hemopoietic marrow, and fat, is immediately transferred to a small dry tube containing a minute amount of powdered heparin† as an anticoagulant. A Wintrobe hematocrit is then filled with the mixture and centrifuged at 2,000 R.P.M. for five minutes. This separates the hemopoietic marrow from the sinusoidal blood and fat. The fat and most of the plasma layer are then pipetted off and discarded. The hemopoietic layer plus a small unit of plasma is pipetted off, placed in a small watch glass, and mixed. Smears are then made in the usual manner, air-dried, and stained with either Wright's stain or with the May-Grünwald-Giemsa combination. When Wright's stain is used, allow the stain to act for three minutes; then dilute with as much distilled water as the slide will hold, mixing very thoroughly. Allow this to stand fifteen to twenty minutes, then wash with distilled water and air-dry. Cell counts also may be made from the mixture.

This method gives a gross approximately quantitative value as well as a constant qualitative bone marrow pattern. Limarzi has followed this method in some 2,675 sternal biopsies. The normal bone marrow pattern has been well defined and the variations from normal, as seen in the various hematologic disturbances, are well noted. Any individual possessing a normal amount of surgical skill can perform the sternal aspiration. Any experienced hematologist can recognize the morphologic appearances of the cells that may be encountered.

Clinically, all the blood disorders that may be associated with pregnancy can be classified in four general groups.

1. Anemia.
2. Conditions associated with enlargement of the lymph nodes, and splenomegaly.
3. Hemorrhagic disorders.
4. Ulcerative lesions of the oral cavity and other mucous membranes, in most instances due to granulocytopenia.

1. Anemia

Anemia is not a diagnosis. It is a symptom. Anemia indicates a decrease in the number of circulating erythrocytes, or reduction in the amount of hemoglobin below the normal standard for the age and sex of the individual. This is purely a peripheral blood evaluation, since anatomically the erythroid tissue may be hypoplastic, normal, or hyperplastic. This paradox is rather common in diseases of the hemopoietic organs.

The anemic state is the result of either (1) a loss of blood from hemorrhage, (2) increased blood destruction, or (3) decreased blood formation.

In recent years, the classification of anemia, based on the size and the hemoglobin content of the average erythrocyte, has proved more satisfactory from the standpoint of treatment than the complicated classifications used in the past. From the hemoglobin, erythrocyte, and hematocrit determinations, an anemia is classified as macrocytic, normocytic, simple microcytic, or hypochromic microcytic in type. (See Table I.)

*University of Illinois sternal needle. Made by V. Mueller & Co., 408 S. Honore St., Chicago, Illinois.

†Powdered Heparin, Lot Number 153. Hynson, Westcott, and Dunning, Baltimore, Maryland.

TABLE I. DETERMINATION OF THE TYPE OF ANEMIA

TYPE OF ANEMIA	MEAN CORPUSCULAR VOLUME (CUBIC MICRONS)	MEAN CORPUSCULAR HEMOGLOBIN (MICROMICROGRAMS)	MEAN CORPUSCULAR HEMOGLOBIN CONC. (PER CENT)	CELL DIAMETER (MICRONS)
Macrocytic	94 and over	More than 27	32 to 36	8.0 to 10.0
Normocytic	80 to 94	27 to 31	32 to 36	*7.5
Simple microcytic	80 and lower	Less than 27	30 or higher	6.0 to 7.0
Hypochromic microcytic	80 and lower	Less than 27	29 or less	6.0 to 7.0

*In familiar hemolytic icterus (spherocytic jaundice) 5.0 to 7.0 microns.

Anemia in Pregnancy

Normal Pregnancy (Physiologic Anemia).—Extensive studies have been made on the peripheral blood in pregnancy. The lowering of the hemoglobin level, erythrocyte count, and hematocrit reading commencing in the third or fourth month, progressing until the sixth or seventh month, and remaining low until delivery, with a return to normal in the puerperium, has been noted and confirmed by all investigators.[9] However, there is no agreement as to the interpretation of these findings. Are these changes due to hydremia or a lack of iron and/or protein deficiency? All agree that a hydremia exists. Dieckmann[10] states that these lowered values are normal during pregnancy and are due to the dilution of the blood by the tremendous increase in the plasma content. Adair and Dieckmann[11] say that only values below hemoglobin 10 grams and erythrocytes 3.36 million are abnormal. Bethell[12] says that hemoglobin 11.3 grams and erythrocytes 3.70 million are the minimum figures. Watson[13] reports that the hemoglobin may fall to 7.7 grams merely from hydremia, while Whitby and Britton[14] is of the opinion that an erythrocyte count below 4.0 million is pathologic. Various investigators have shown definite improvement in these blood values in cases treated with iron in comparison to control cases.[15] Others[16] have failed to note this improvement.

At its best, the peripheral blood is not always a true index of the hemopoietic state. The findings in the peripheral blood are too readily influenced by the physiologic reaction to food, muscular work, and emotional upsets. Likewise, hematologic technique is such that great error is possible in the performing of these seemingly simple tests. It has been shown that the error involved in the hemoglobin estimation via the Newcomber method is about 5 per cent. In normal patients the hemoglobin level may vary up to 15 per cent (2.07 grams) during the day. The erythrocytes may fluctuate within a 17 per cent range during the day, whereas, the potential error in the method of performing the count may vary from 2 to 13 per cent.[17] With such frequent variations and possible errors present, one must be hesitant to state that a pregnant woman who already possesses a lowered hemoglobin level and erythrocyte count from the hydremia or increase in the plasma content is anemic. Likewise, all results from therapy must not be overrated.

The bone marrow, however, is stable. The findings in normal pregnancy are constant. We have previously reported[18] our findings in a group of patients studied throughout pregnancy and others seen at various intervals of their pregnancy. In all cases, we noted a normal erythroid pattern. A slight

myeloid hyperplasia plus a tremendous increase in the megakaryocytes was present. In general, the bone marrow was hyperplastic throughout pregnancy, but qualitatively the erythroid development was normal. Correlative studies with the peripheral blood were made in all cases. We noted the same peripheral blood changes as found by other investigators.

The bone marrow rapidly reacts to changes in the peripheral blood. The loss of iron, be it due to its direct loss via bleeding, decreased absorption, or an increase in blood destruction, immediately stimulates the bone marrow to a greater effort. Earlier forms of erythroid cells predominate the marrow cells. This is called a normoblastic erythropoiesis and is a constant feature of such an anemic state.[19] A normal bone marrow pattern is direct evidence of a normal blood picture. Anemia is never present when one sees such a bone marrow finding.

Therefore, we are definite in our opinion that the changes in the peripheral blood noted in normal pregnancy are merely due to the hydremia, and possess no relation to an anemic state. No treatment of any type is necessary. In suspect cases of anemia with peripheral blood levels below those given for normal pregnancy, the bone marrow pattern will determine whether one is dealing with an increase in the hydremia or the presence of a true anemia.

Iron Deficiency Anemia.—Many of these patients, exhibiting a lowering of the peripheral blood values below the minimum just mentioned, possessed bone marrows that showed a true normoblastic erythropoiesis in contrast to that as above described. Pronormoblasts and basophilic normoblasts were seen in large numbers. These cells represent a more immature type of erythroid development, and are the response of the bone marrow to the lack of iron independent of the cause. These patients promptly improved on adequate iron therapy and did not improve without treatment. With treatment, both the peripheral blood and bone marrow returned to the normal levels noted during pregnancy.

Thus, this normoblastic bone marrow readily denotes the presence of a true anemia and determines the type of treatment needed.

Megaloblastic Anemia (Pernicious Anemia of Pregnancy).—This anemia, although not common, is so severe, produces such a severe anemia, and responds so well to appropriate therapy, that its diagnosis must be considered in any severe anemic state associated with pregnancy. In patients with a severe anemia in which the cell size is definitely large (mean corpuscular volume over 100 cubic microns), the cell well filled with hemoglobin (mean corpuscular hemoglobin concentration, 32 per cent), and macropolycytes noted in the peripheral blood, the diagnosis is fairly obvious. However, as previously reported[18] in three cases which we have seen, the peripheral blood findings varied in each case. Only one was typical of this anemia. The second was that of a normocytic anemia, and the third, that of a microcytic hypochromic anemia. Yet, in all cases, the sternal marrow analysis showed a typical megaloblastic marrow. Davidson[20] has reported similar observations. Adequate liver therapy and blood transfusions are lifesaving to these patients. Iron is futile except as an adjunct when the hemoglobin concentration is low.

The importance of an accurate diagnosis is readily apparent. We feel that one cannot truly diagnose this type of anemia from the peripheral blood alone. The findings are often confusing, whereas the sternal marrow aspiration is diagnostic.

Aplastic Anemia.—This severe anemia is essentially characterized hematologically by an anemia, leucopenia, and thrombocytopenia, and clinically by a marked waxy pallor, absence of enlargement of liver, spleen, or lymph nodes, and an acute fatal course. The bone marrow reveals a marked hypoplasia of all cellular elements. Occasionally, bleeding tendencies predominate the clinical picture, and thus lead to diagnostic error. This also occurs when ulcerative lesions of the oral cavity accompany the symptoms. Sternal marrow biopsy is diagnostic and will rule out the suspected purpura or agranulocytosis. Aplastic anemia may be primary (idiopathic) or secondary.

Secondary aplastic anemia is caused by chemicals and physical agents such as roentgen-ray and radioactive substances; and systemic diseases such as nephritis, metastatic carcinoma, sarcoma, Hodgkin's disease, and lymphatic leucemia, which either destroy or invade and replace the normal bone marrow elements. Sternal puncture is of aid in the diagnosis of such primary conditions.

Primary aplastic anemia, fortunately, is not common during pregnancy. Hurwitt and Field[21] reported one such case and reviewed the literature in thirteen others. They are of the opinion that pregnancy may cause this hypoplasia of the bone marrow with its resultant peripheral blood findings. They report a case of Nieuwenhius with such bone marrow findings. The pregnancy was terminated and recovery followed. The bone marrow revealed cellular elements four days after delivery. Of the fourteen cases studied, there were five survivals. In these, the patients all had the uterus emptied either spontaneously or by induction. Any patient who is pregnant and presents diagnostic evidence of an aplastic anemia with a hypoplastic bone marrow should have the pregnancy terminated at once. Repeated blood transfusions should be given until the bone marrow gives evidence of recovery.

However, until more cases are studied during pregnancy, one should make a poor prognosis, as most cases of primary aplastic anemia possessing a hypoplastic bone marrow run a rapidly fatal course, irrespective of treatment.

Occasionally, the bone marrow findings in cases of primary aplastic anemia reveal a hyperplastic bone marrow. This is the so-called pseudo-aplastic anemia. The course here is more chronic, and repeated blood transfusions may carry the patient along for some time. A pregnant individual may thus be carried until the fetus becomes viable. Frequent marrow analyses will aid in determining how long one may persist in an expectant attitude.

In secondary aplastic anemia, the prognosis depends upon the causative agent plus the bone marrow findings. The presence of a hypoplastic marrow is always grave. The causative disease in itself may be a fatal one. If so, one should treat the patient paliatively and allow the pregnancy to proceed, in the hope that a living child may be salvaged. Termination of the pregnancy will not alter the progress of the primary disease. Removal of the cause such

as chemical (arsenical, sulfonamides, etc.) or physical agents may be of aid. When such a cause is present, the conduct of the pregnancy will be determined by the bone marrow findings. Hypoplastic marrow—termination of the pregnancy; hyperplastic marrow—removal of the cause, repeated blood transfusions, and a conservative attitude toward the pregnancy.

Sternal marrow biopsy is thus an essential examination in all cases of suspected aplastic anemia. The findings are of great prognostic as well as diagnostic value.

Hemolytic Anemia.—Hemolytic anemia may be either intrinsic or extrinsic in character. The intrinsic anemias include *congenital* and *acquired hemolytic anemia, sickle-cell anemia,* and probably *Cooley's anemia* and erythroblastosis which, in many instances, has been shown to be associated with the Rh factor. A hemolytic anemia is sometimes seen associated with neoplasms, Hodgkin's disease, leucemia, and infections.

The bone marrow shows a normoblastic hyperplasia in these anemias. Sternal marrow biopsy is only of a "negative" value in that it rules out other types of blood disorders and encourages one toward further study of the disease; e.g., the search for the sickle-cell phenomena.

Congenital hemolytic anemia (spherocytic jaundice) is characterized by an anemia, a palpable spleen, an increase in the reticulocytes, and a lowered resistance of the erythrocytes to hemolysis in hypotonic salt solution. The red blood cells are spherical and small in diameter measuring five to seven microns (normal 7.5 microns). Pregnancy does not effect the course of the disease, since mothers have borne several children without any ill effects. Splenectomy results in a clinical cure.

Drugs, chemicals, certain parasites, and bacteria produce a hemolytic anemia. The hemolytic anemia that occurs during the administration of the sulfonamides produces a rapid and progressive drop in the hemoglobin and erythrocytes, a reticulocytosis, and a myeloid immaturity in the peripheral blood. The bone marrow shows a marked hyperplasia of the normoblastic tissue in all the hemolytic anemias secondary to increased blood destruction.

In general, the sternal marrow biopsy is not in a sense diagnostic in the hemolytic anemias but, in demonstrating the normoblastic erythroid response to the increased blood picture, does form a part of the diagnostic chain. Repeated blood transfusions and a conservative attitude toward the pregnancy are in order. Removal of the cause, as in the case of drugs, chemical, bacteria, and parasites, is of course, essential. Splenectomy following the delivery of the baby should be considered when indicated.

Elliptical red corpuscles, or ovalocytosis, is a hereditary trait transmitted by either sex, possibly as a simple Mendelian dominant. One case in a colored pregnant woman was accidentally observed. Except for the large member of elliptical red corpuscles, the blood studies were normal. The bone marrow was normal, and the ovalocytes seen in the marrow smear were probably due to dilution with peripheral blood. The anomaly of the red cells does not occur until after the nucleated red cells in the bone marrow extrude their nuclei.

Case Report

M. D., a 28-year-old gravidi ii, para i, was seen in the obstetric clinic on Aug. 15, 1938. Her last menses occurred on June 17, 1938. She appeared to be in good health, and pelvic examination revealed a six weeks intrauterine pregnancy. The past history was negative, except for the presence of symptoms of hyperthyroidism in 1932, which were relieved by a thyroidectomy in 1934. Her first pregnancy (in 1936) was uneventful. Labor was somewhat prolonged because of a generally contracted pelvis, and was terminated by a midforceps delivery. The child was normal and healthy. The congenital blood abnormality was not noted during the first pregnancy, but was found at the initial examination during the second. The essential blood findings were: hemoglobin, 10 Gm.; erythrocytes, 3,360,000; hematocrit, 29 per cent; icterus index, 10 units; platelets, 246,000; and reticulocytes, 2 per cent. The differential blood smear showed normal leucocytic findings. Seventy-four per cent of the erythrocytes were elliptocytes. The bone marrow was normal. A spontaneous abortion terminated the pregnancy on Sept. 8, 1938. The husband's blood was normal. The one child, aged 17 months, had 6 per cent ovalocytes in the blood smear. Sickling phenomena was not noted.

2. Enlargement of the Lymph Nodes and Splenectomy

Acute and chronic infections of the head and neck are the most common causes of localized lymphadenopathy. The peripheral blood usually shows a leucocytosis with a preponderance of young toxic granulocytes (shift to the left). Occasionally a leucopenia is present. The bone marrow shows a mild myeloid hyperplasia. Sternal marrow biopsy here would merely eliminate the possibility of a blood dyscrasia.

Infectious mononucleosis, or glandular fever, is not uncommon, and may occur during pregnancy. The presence of atypical lymphocytes (not monocytes) in large numbers in the peripheral blood are diagnostic but may lead to the suspicion of a leucemia. The bone marrow is hyperplastic with a moderate to marked granulopoietic immaturity. This is never carried to the stage of myeloblastic involvement. The heterophile antibody reaction is usually positive, but occasionally may be negative. When this occurs, sternal aspiration will rule out the suspicion of a leucemia.

Leucemia.—The leucemias may be divided into acute and chronic leucemia, and subleucemic types. Cases which live six months or less are said to be acute, the remainder are chronic. Subleucemia is used when the total leucocyte count is low or practically within normal limits. The leucemic state may be (1) myelogenous, a disorder of the bone marrow characterized by abnormalities of granulocytic formation; (2) lymphatic, a disorder of lymphatic formation; and (3) monocytic, characterized by the presence of normal and immature monocytes in the peripheral blood plus a hyperplasia of the reticulo-endothelial system. Only the myeloid and lymphatic types have been observed during pregnancy. Recent investigators have found 79 true cases reported in the literature.[22]

The diagnosis of leucemia is usually obvious from the clinical symptoms and the peripheral blood findings. Sternal marrow biopsy is merely confirmatory. However, a not too uncommon type of leucemia is the subleucemic type. Here the blood merely shows a mild anemia and often a leucopenia. Abnormal (immature) forms may be few or absent. The sternal marrow will be filled

with highly immature leucocytes. Sternal aspiration here is diagnostic as the peripheral blood findings may be obscure. Alt[23] has reported just such a case.

The pregnancy should be followed conservatively in a leucemic patient in the interest of the child, since leucemic mothers give birth to normal children.[22] All forms of leucemia are invariably fatal. An adequate diet, liver, iron in large doses, vitamins (especially the B complex), and rest in bed during the acute exacerbation are of help. Arsenic therapy in the form of Fowler's solution (liquor potassium arsenite), roentgen-ray therapy to the spleen or affected lymph nodes (except in the acute and leucopenic phase), and frequent blood transfusions are all of temporary value. Radioactive phosphorus has recently proved of value in the treatment of chronic myeloid leucemia, but it is not curative.

Chronic Myeloid Leucemia (Case Report)

Mrs. A. B., aged 21 years, entered the hematology clinic on April 20, 1938. She was referred to this clinic for treatment of chronic myelogenous leucemia. The diagnosis was confirmed by the hematologic investigation (see Table II). She was always in good health until the onset of the present illness. When she was sixteen years of age, she gave birth to her first child. The pregnancy and labor were normal. Two years later, she delivered a second child and again the pregnancy was uneventful. Shortly after this she complained of pain in the left lower costal region. An enlarged spleen was palpated and the blood dyscrasia diagnosed. Roentgen-ray therapy to the spleen was given at another hospital. Two years later she delivered her third child. She was exceedingly weak and noted ankle edema during this pregnancy. Labor was rapid and normal. Following her initial visit

TABLE II. CHRONIC MYELOGENOUS LEUCEMIA

	BEFORE PREGNANCY	PREGNANT AT TERM	4 DAYS POST PARTUM	6 MONTHS POST PARTUM
Hemoglobin (grams)	9.5	9.75	10.25	
Erythrocytes	3,500,000	3,800,000	3,410,000	
Leucocytes	250,000	105,000	60,000	250,000
Hematocrit (R %)	29	31	30	
Hematocrit (W %)	13.5	3.5	3.0	
Sedimentation (mm./hr.)				
Uncorrected	28	45	50	
Corrected	8	24	26	
Icterus index (units)	5	5	5	
Reticulocytes (%)	0.9	0.5	0.3	
Platelets	increased	normal	normal	
M.C.V. (c.u.)	89.2	81	88	
M.C.H. (m.m.)	29.2	26	30	
M.C.H.C. (%)	32.7	31	34	
Differential smear (%)				
Myeloblasts	0	1	0	
Eosinophilic myelocytes	1	0	0	
Promyelocytes	3	0	0	
Myelocytes	2	16	10	
Metamyelocytes	35	5	7	
Stab forms	0	12	7	
Polymorphonuclear neutrophils	51	55	67	
Lymphocytes	2	1	1	
Monocytes	0	2	2	
Eosinophils	2	4	3	
Basophils	4	4	3	

Bone marrow—Hyperplastic
Predominant granulopoietic elements

R = red cells. W = white cells. M.C.V. = mean corpuscular volume. M.C.H. = mean corpuscular hemoglobin. M.C.H.C. = mean corpuscular hemoglobin concentration.

to the hematologic clinic she received some roentgen-ray therapy (650 r. in four treatments) to the spleen. She next returned to the hospital on July 10, 1939, pregnant and near term. Except for the presence of the leucemia, her general health appeared good. An episode of mild vaginal bleeding occurred. When she was three weeks past term, medical induction was attempted, but this was unsuccessful. Labor was then induced by means of a Voorhees bag, and a normal delivery of a 2,980-gram healthy infant occurred six hours later. The puerperium was uneventful. Since then, she has received roentgen-ray therapy to the spleen on several occasions. When last seen her general health was fair and the leucemic state still chronic. All children are healthy, none showed any type of blood disorder.

Splenomegaly without lymphadenopathy has been reported many times during pregnancy.[24] Enlargement of the spleen is observed in most diseases of the hemopoietic organs, in circulatory disturbances, infections, metabolic disturbances, primary tumors, and in a number of unclassified conditions.

Banti's disease is a condition characterized by splenomegaly, anemia, leucopenia, and, in many cases, by a thrombocytopenia. When the condition has progressed to a later stage, cirrhosis, jaundice, and ascites complete the picture. Several theories have been suggested as the cause of the disease, an infectious process as the causative agent, and mechanical factors producing the symptom complex. In this group of conditions are included *idiopathic splenomegaly, splenic anemia,* and *thrombophlebitis of the splenic or portal veins* which are considered as phases of the same disease process.

The bone marrow in Banti's disease and closely allied conditions in the earliest stage shows a myeloid hyperplasia and there is an anemia and leucopenia in the peripheral blood. Later in the disease, the bone marrow shows a maturation arrest of the myeloid and megakaryocytic tissue with a leucopenia, neutropenia, thrombocytopenia, and myeloid immaturity in the peripheral blood.[25]

Pregnancy under such conditions should be allowed to proceed in the usual manner. Following delivery of the child, splenectomy should be strongly considered, since the removal of the spleen, even in the later stage described, will restore the bone marrow and the peripheral blood to normal. On the other hand, in the last stages of the disease when cirrhosis of the liver is present, the bone marrow biopsy shows a marked erythroid immaturity as well as the above changes in the myeloid tissue. The presence of these findings speaks against splenectomy, as the results here are poor.

Banti's Disease (Case Report)

M. D., a 25-year-old gravida iii, para ii, was seen in the sixth month of her pregnancy on July 25, 1944. For the past month she complained of an aching pain in the left side of her upper abdomen. The spleen was found to extend four fingers breadth below the costal margin. This patient was referred in consultation by Dr. Robert E. Lee, who has continued to care for the patient. The blood findings are shown in the accompanying table. The pregnancy proceeded uneventfully followed by a normal spontaneous delivery on Oct. 12, 1944. The patient and the child are both in excellent health.

We have a second case under observation in which the spleen had been removed previously because of Banti's disease. During the pregnancy, the patient developed an anemia which has responded to iron therapy and repeated blood transfusions. She is being allowed to proceed with the pregnancy. Multiple vitamins, including vitamin K,

TABLE III. BANTI'S DISEASE

Hemoglobin (grams)	9.5
Erythrocytes	3,740,000
Leucocytes	5,000
Hematocrit (%)	37
Sedimentation (mm./hr.)	
Uncorrected	30
Corrected	20
Icterus index (units)	7.5
Reticulocytes (%)	3.2
M.C.V. (c.u.)	98
M.C.H. (m.m.)	26
M.C.H.C. (%)	27
Platelets	adequate
Differential smear (%)	
Stab forms	5
Polymorphonuclear neutrophils	71
Lymphocytes	20
Monocytes	2
Eosinophils	2
Basophils	0

Bone marrow—Myeloid hyperplasia
No malarial parasites in blood or bone marrow

liver extract intramuscularly, and choline are being given to protect the liver. Liver function tests and blood protein determinations are being made at repeated intervals.

In most instances a generalized progressive enlargement of the lymphoid tissue speaks for malignant neoplastic disease. A practically normal white cell count in an individual with enlargements of the lymph nodes with or without a splenomegaly is suggestive of *Hodgkin's disease or lymphosarcoma.* These two conditions fall into the group of diseases called *lymphoblastoma* which include *lymphatic leucemia* and *mycosis fungoides.* Except for lymphatic leucemia, a biopsy of lymph nodes is required for a final diagnosis.

In *Hodgkin's disease,* the bone marrow is usually hyperplastic and of a myeloid or megakaryocytic type, depending upon the stage and severity of the process. An increase in the number of plasma cells, histocytes or reticulum cells, and eosinophiles are observed during some phase of the fatal condition. An anemia is present in the peripheral blood. Pregnancy is not affected by, nor does it affect, this chronic slowly progressive disease. The pregnancy may be treated in a conservative manner. Roentgen-ray therapy to the affected lymph nodes may prolong the course of the disease.

Hodgkin's Disease—Case Reports

CASE 1.—Mrs. L. K., a 20-year-old gravida i, para 0, entered the obstetric clinic on April 30, 1938, for prenatal care. Her last menses began on Feb. 16, 1938, and the expected date of delivery was Nov. 23, 1938. She was found to be about two and a half months pregnant. The past history was essentially negative, except for one visit to the clinic on Feb. 3, 1938, because of recurrent sore throats and swollen glands in the neck. At this visit in February, the ear, nose, and throat department did not find any pathology. On the first prenatal visit she appeared to be in good health and routine pregnancy care was advised. The blood findings are shown in the accompanying table. On June 21, 1938, when the patient was five months pregnant, a cervical adenitis was noted. Hematologic studies were performed, and the findings of anemia in the peripheral blood noted. The bone marrow showed a normal erythroid pattern, a myeloid hyperplasia, and an increase in the megakaryocytes. A biopsy of a cervical

TABLE IV. HODGKIN'S DISEASE. CASE 1

	3 MO. PREG.	5 MO. PREG.	1 YR. LATER	5 YR. LATER
Hemoglobin (grams)	70%	9.8	70%	60%
R.B.C.	3,850,000	3,200,000	4,010,000	3,450,000
W.B.C.	17,700	10,050	11,700	9,900
Hematocrit (%)		30		
Sedimentation (mm./hr.)				
Uncorrected		62		
Corrected		34		
Icterus index (units)		2.5		
Reticulocytes (%)		1.1		
Platelets		350,000		
M.C.V. (c.u.)		93		
M.C.H. (m.m.)		30		
M.C.H.C. (%)		30		
Differential smear (%)				
Metamyelocytes		1		
Stab forms		28		
Polymorphonuclear neutrophils		54		
Lymphocytes		12		
Monocytes		4		
Eosinophils		0		
Basophils		1		

Bone marrow—Myeloid hyperplasia
Normal erythropoiesis
Increase in megakaryocytes

gland revealed the typical pathologic picture of Hodgkin's disease. Pregnancy was uneventful, and on Oct. 23, 1938 (36 weeks), a 2,550-gram girl was spontaneously delivered following a rapid, normal labor. This patient has been seen at frequent intervals since then and has run a chronic slowly progressive downhill course (See Table IV).

CASE 2.—A. A., a 32-year-old gravida i, para 0, was well until 1935 (aged 27 years) when she noticed a large nodule in her neck and in the axillary region. Biopsy of the cervical node showed the presence of Hodgkin's disease. She received small amounts of roentgen-ray treatments to these nodes in 1939. Pregnancy occurred in 1940. A 2,430-gram healthy infant was delivered spontaneously at term on Sept. 1, 1941, following an

TABLE V. HODGKIN'S DISEASE. CASE 2

	BEFORE PREG. 11/16/39	DURING PREG. 3/8/40	4 YR. LATER 12/19/44
Hemoglobin (grams)	9.75	10	8
Erythrocytes	4,210,000	4,750,000	3,600,000
Leucocytes	19,600	16,300	26,400
Hematocrit (%)	34	34	27
M.C.V. (c.u.)	81	71	75
M.C.H. (m.m.)	23	21	22
M.C.H.C. (%)	29	27	21
Icterus index (units)	2	5-7.5	0
Reticulocytes	0.3	0.5	0
Sedimentation (mm./hr.)			
Uncorrected	59	55	47
Corrected	36	38	19
Differential smear (%)			
Stab forms	8	30	12
Polymorphonuclear neutrophils	73	51	80
Lymphocytes	11	10	8
Monocytes	8	7	0
Eosinophils	0	2	0
Basophils	normal	normal	normal

Bone marrow—Myeloid hyperplasia
Increased megakaryocytes
Normoblastic erythropoiesis

uneventful pregnancy and a normal labor. The course since then has been a chronic progressive downhill one. At the present time the patient is hospitalized because of anemia and a low grade febrile state (see Table V).

Lymphosarcoma spontaneously, or following roentgen-ray therapy may be converted into a condition called *leucosarcoma.* Here the bone marrow cells are invaded and replaced by the malignant cells. This is reflected in the peripheral blood by an anemia, granulopenia, and thrombocytopenia.

3. Hemorrhagic Disorders

Hemorrhagic diseases may occur during pregnancy. The tendency to bleed from mucous membranes and into the skin with the formation of petechiae and ecchymoses may be the symptom of an underlying disease or the bleeding manifestation itself may be the primary feature of the disease.

The mechanism in abnormal bleeding usually involves one or more of the following factors: (1) quantitative or qualitative changes of the platelets; (2) disturbances in the clotting mechanism; and (3) increased permeability of the capillary wall. In general, three tissues are primarily concerned in hemorrhagic disorders. They are the bone marrow megakaryocytes, which produce the blood platelets and in turn furnish the thromboplastin; the liver, which supplies the prothrombin, heparin, and fibrinogen; and the blood vessels, with their endothelial function and capillary reactions. The spleen is a disturbing factor in some thrombocytopenic states, and the gastrointestinal tract participates in the mechanism of vitamin K formation and absorption.

The term *thrombocytopenic purpura* is used to describe all cases presenting episodes of spontaneous bleeding from the mucous membranes and into the skin. This may be primary (without a known cause) and termed essential idiopathic thrombocytopenic purpura or it may be secondary.

In *primary idiopathic thrombocytopenic purpura* the bleeding time is prolonged. The coagulation time may be normal, but the clot retraction is poor. A differential smear or platelet count reveals the small number of blood platelets. These findings plus the clinical history makes the diagnosis obvious.

The bone marrow findings are essential as a guide to therapy. Where one finds an abundance of megakaryocytes in the bone marrow the prognosis is good. It is not known why this paradox of an absence of platelets in the peripheral blood and an increase of megakaryocytes in the marrow should occur. Some feel the spleen is disintegrating the platelets at too great a rate; but Limarzi[26] feels that the megakaryocytes are developing abnormally and thus cannot get out into the circulation. Patients with bone marrow findings, as described, respond rapidly to splenectomy. The peripheral blood and the bone marrow returns to normal and the bleeding tendencies disappear.

Many cases of essential thrombocytopenic purpura have been followed during pregnancy.[27] Splenectomy has been reported during pregnancy.[28] We feel that one should adopt a conservative attitude toward the pregnancy. Adequate diet, bed rest as needed, and repeated blood transfusions of fresh blood to keep up the peripheral blood levels should be administered during

the pregnancy. Splenectomy is best done following the pregnancy and during a remission of the disease, but may be performed if the patient is seen during the first trimester.

Purpura (Case Report)

B. P., an 18-year-old gravida i, para 0, entered the hospital because of a severe nosebleed with evident loss of blood. Examination revealed evidence of the nasal bleeding plus blood colored gingival margins. The patient stated that following an appendectomy in 1938 she had often noted attacks of bleeding from the gums, nose, rectum, and into the skin. These attacks had of late been increasing in severity and intensity. On the date of admittance (June 20, 1940) she was found to be in the sixth month of her pregnancy. Her last menses began on Dec. 17, 1939, and her expected date of delivery was Sept. 20, 1940. Her pregnancy had been uneventful to the day preceding admission, when nasal bleeding occurred (except for an occasional spell of nausea and vomiting in the first trimester and slight bleeding from the gums). The hematologic findings are shown in the accompanying tables. Bed rest, nasal packing, and two 500 cubic centimeter transfusions

TABLE VI. PRIMARY THROMBOCYTOPENIC PURPURA

	6 MONTHS	8 MONTHS	20 DAYS POST PARTUM	AFTER SPLENECTOMY
Hemoglobin (grams)	9.8	10	14.5	17.5
Erythrocytes	3,120,000	3,250,000	4,810,000	5,910,000
Leucocytes	17,150	9,200	9,950	9,550
Hematocrit (%)	26	32	44.5	58.5
Bleeding time (min.)	2.5	3	3	3
Coagulation time (min.)	9	15	15	15
Clot retraction (min.)	90	60	48 hr.	0
M.C.V. (c.u.)	83	98	92	98
M.C.H. (m.m.)	31	30	30	29
M.C.H.C. (%)	37	31	32	30
Reticulocytes (%)	7	1	0.8	1.0
Icterus index (units)	5	5.75	5	7.5
Sedimentation (mm./hr.)				
Uncorrected	65	60	25	1
Corrected	29	40	28	19
Platelets	115,000	190,000	40,000	200,000
Differential smear (%)				
Myelocytes	4	0	0	0
Stab forms	20	10	6	6
Polymorphonuclear neutrophils	50	65	65	64
Lymphocytes	7	14	19	11
Monocytes	14	9	5	11
Eosinophils	5	2	3	5
Basophils	0	0	2	3
Bone marrow—Myeloid hyperplasia Normoblastic erythropoiesis Megakaryocytes increased				

of whole blood stopped the bleeding and improved the blood picture. Frequent small blood transfusions were given weekly until delivery. The pregnancy then proceeded uneventfully, and a normal female child was delivered spontaneously at term (Sept. 29, 1940) after a normal labor. The third stage was short and uneventful, the total blood loss being 150 cubic centimeters. Five hundred cubic centimeters of whole blood was given immediately after delivery. Puerperium was uneventful. Splenectomy was performed on Oct. 23, 1940. The spleen weighed 239 Gm., and the pathologist's report was "spleen consistent with thrombocytopenic purpura." Complete recovery followed.

Occasionally in essential thrombocytopenic purpura with clinical and peripheral blood findings as described, the bone marrow will show a hypoplasia of the megakaryocytes: Here one is dealing with a form of thrombocytopenic

purpura in which splenectomy will fail to be of any value. This type usually runs an acute rapidly fatal course. Perhaps the uterus should be emptied in this "malignant" form of thrombocytopenic purpura.

Secondary or symptomatic thrombocytopenic purpura may be due to other conditions. Numerous classifications of the purpuric states have been presented. The common characteristic of all purpuras other than the primary type is the presence of a causative factor.

Many purpuric states are merely symptoms of other blood dyscrasias such as aplastic anemia, leucemia, leucosarcoma, etc., as previously described. The predominant bleeding factor plus inconclusive evidence in the peripheral blood may lead to an incorrect diagnosis. Sternal aspiration will be the key to the diagnosis.

Bleeding tendencies are often noted as due to drug idiosyncrasies (such as belladonna, quinine, and sulfapyridine). Here clot retraction is normal, as is the bone marrow.

The sternal bone marrow findings in these hemorrhagic disorders tend to denote the presence or rule out the existence of a true blood dyscrasia, and in true primary idiopathic thrombocytopenic purpura offers a guide to treatment.

4. Ulcerative Lesions of the Numerous Membranes, Especially the Oral Cavity

Ulcerative lesions of the oral cavity and other mucous membranes are a common finding in a group of conditions called granulocytopenia or agranulocytosis. Granulocytopenia is classified as primary or secondary.

The primary type is characterized by a marked reduction in the white count (leucopenia) and a few and sometimes no granulocytes (neutropenia) on blood smear examination. The other blood elements are not affected. The patient feels extremely ill and looks toxic. The lymph nodes of the neck are frequently enlarged. Soreness of the throat, ulceration and necrosis of the mouth and pharynx occurs. These lesions may occur in the mucous membranes of any part of the body.

The pharynx appears diffusely purplish red, thus differing from the bright red and streaked throat of acute tonsillitis. This suggests breaking down of the tissue in the absence of polymorphonuclear neutrophils. The mortality in the acute cases in some series is as high as 90 per cent. Among the causes of granulocytopenia are drugs, fatigue, and infections. The drugs include amidopyrine (pyramidon), dinitrophenol, arsenicals, gold salts, sulfanilamide, and related compounds. Most of these agents are secondary causes of granulocytopenia. More often no cause can be found for the primary malignant neutropenia. The bone marrow shows aplasia or a hyperplasia with a maturation arrest of the myeloid series. The chance of recovery from the disease is best in patients showing a maturation arrest of the granulocytic tissue and a pronounced and sustained monocytosis in the peripheral blood. The therapeutic agents that are used in the treatment include stimulating doses of roentgen ray, adenine sulfate, pentnucleotide, liver extract, iron, yellow bone marrow concentrates, leucocytic extract, and small transfusions of fresh blood.

Inflammatory changes in the oral cavity, such as ulcerations and necrosis with membrane formation, and a leucopenia and neutropenia, can occur in acute poisoning, acute and chronic leucemia, aplastic anemia, sespis, diphtheria, and infectious mononucleosis.

Besides pale and bleeding gums, the lesions in leucemic processes involving the mouth include swelling, hypertrophy and destruction of the interdental tissue following necrosis. These changes in the oral cavity may resemble those seen in patients with scurvy, acute stomatitis due to a variety of conditions, and Vincent's infection. Necrosis of the mucous membranes of the oral cavity is seen on the palate, cheeks, lips, and gums. Necrotic lesions of the tonsils and pharynx occur in acute leucemia.

Acute follicular tonsillitis, peritonsillar abscess, diphtheria, tuberculosis, syphilis, and fusospirochetal disease will not be confused with leucemia and other conditions that cause leucopenia, neutropenia and ulcerations of the oral cavity if the following factors and examinations are kept in mind: (1) careful inquiry concerning the use of drugs, (2) history of exposure to overdosage of roentgen rays or radioactive substances, (3) detailed blood and bone marrow studies and (4) laboratory aids such as blood cultures, bacteriologic studies of the oral lesions, sputum examinations, blood Wassermann reaction, and several of the tests previously mentioned.

Summary

In the past, the obstetrician's main interest in the blood findings associated with pregnancy has been in the clinical interpretation of the commonly noted lowered hemoglobin level and erythrocyte count seen in healthy individuals during pregnancy. In more recent years, the association of pregnancy and the various blood disorders has gained his attention, but unfortunately he has not made use of the sternal marrow findings. The hemotologist, likewise, has not yet considered the problems of pregnancy in the light of the information obtained from bone marrow studies. It is only through cooperation of the hematologist and the obstetrician that such a relatively new procedure can reach its proper place in clinical investigation.

Bone marrow biopsy is not the sole method or answer to hematologic diagnosis. Although it is merely a part of the diagnostic "blood work-up" it is a most important one. The standard peripheral blood studies are still of major importance, and in many cases the sternal marrow findings may be only confirmatory. Yet, peripheral blood studies, especially in pregnancy because of the hydremia factor, often do not give one sufficient information, or may even give a false clue to diagnosis. Sternal marrow biopsy then becomes mandatory.

Sternal marrow aspiration (puncture method) using the concentration technique enables one to obtain a gross impression of the state of the bone marrow; and the well-developed "sternal hemogram" reveals more than enough marrow cells to enable the hematologist to readily discern the bone marrow pattern.

The normal erythroid marrow findings noted in healthy patients during pregnancy are conclusive in revealing that the lowered peripheral blood levels are due only to a hydremia, and speak for normal findings during pregnancy associated with blood dilution.

The characteristic marrow pattern noted in the various blood dyscrasias is of diagnostic, prognostic, and therapeutic importance in the management of both the hematologic and obstetric problems.

One of the greatest values of sternal marrow biopsy is its "negative value." The finding of a normal type of bone marrow definitely rules out the presence of a primary blood disease. The only exception is in cases of aleucemic lymphadenosis. (Lymph node biopsy will be needed.)

Conclusions

1. The cooperation of the hematologist and the obstetrician is essential to the proper management of blood disorders during pregnancy.

2. Sternal puncture with the concentration method of analysis is the preferred technique during pregnancy.

3. Sternal marrow analysis is an essential procedure in the diagnosis of the blood disorders associated with pregnancy.

4. Sternal marrow analysis is often the key to diagnosis and the guide to prognosis, and therapy both from the viewpoint of the hematologist and the obstetrician.

5. A group of illustrative blood disorders occurring during pregnancy are reported.

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Discussion

DR. HENRY L. SCHMITZ.—There has been considerable discussion concerning the relative value of the trephine method and the aspiration method of bone marrow biopsy. Limarzi's technique, which Dr. Wolff has employed, overcomes the objection of dilution in the aspiration method, but I think it should be pointed out that certain other objections can be raised. These objections are that the material withdrawn by aspiration may not be representative, that the cells do not retain their original relationships, and that the cells may not retain their relative proportions. Because of these factors, it is conceivable that one may get a false impression concerning hyperactivity, hypoplasia, or defective maturation of cells. In spite of these objections, we feel that the method is of unquestioned value if the results are used in conjunction with other clinical and laboratory findings. Most of the objections enumerated can be overcome if the aspiration is repeated whenever there is any question about the findings.

The value of bone marrow studies in interpreting the blood picture in health and disease is illustrated especially well, I think, by the findings in normal pregnancy. I have the feeling, although I have no actual figures to support this view, that true iron deficiency anemia is probably more frequent in pregnancy than Dr. Wolff's paper would lead us to believe. One gets this impression also from the reports of Gasul, Heath, Bethel, and others. If we consider the many possible etiologic factors, I think it is surprising that anemia does not occur more frequently. First, there is the increasing demand on the part of the fetus for iron and for red cell forming materials. Second, there are a number of factors that tend to limit the supply of these materials. Gastrointestinal disturbances which interfere with the ingestion of food are frequent. There are various toxic manifestations which may necessitate restriction of certain articles of food. Especially during the depression, there were many clinic patients who were on inadequate diets because of financial reasons. Finally, even when the intake of food is adequate, there may be deficient absorption or utilization of iron, as Strauss and Castle pointed out, due to hypo- or achlorhydria. All these factors disturb the normal balance that exists between the demand for and the supply of iron. I do not think we can draw a sharp line of demarcation between normal and abnormal blood findings in pregnancy. The values in nonpregnant women vary too much. A woman with a normal hemoglobin of 12.5 Gm. may have a reduction to 10 Gm. in pregnancy, which can be accounted for by hydremia. However, in a patient with a normal of 15 Gm., a reduction to 10 Gm. would make one think of a hypochromic anemia. I do not think it is desirable to do routine bone marrow punctures in pregnancy. It seems to me it is sound practice to administer small doses of iron to the pregnant woman in order to forestall the occurrence of an iron deficiency anemia. Another reason for administering pro-

phylactic doses of iron is the possibility that the infants born of anemic mothers are more likely to develop iron deficiency anemia during the first year of life, due to inadequate storage of iron in utero.

DR. HOWARD L. ALT.—Dr. Wolff has learned very well the language of the hematologist. His paper is an excellent review of the fundamentals of hematology and should help greatly in solving some of the hematologic problems that occur during pregnancy.

As a routine procedure, the sternal puncture should not be done before the patient is adequately worked up. In most cases, a diagnosis can be made from the history, physical examination, and a complete study of the peripheral blood picture. If then there is a question as to the exact diagnosis, the sternal marrow will often give the additional information needed.

I should like to emphasize the wide variations in the red count and hemoglobin value that occur in normal adults. Similar variations occur during pregnancy, but at a 20 per cent lower range. Thus a red count of 3.5 million and hemoglobin of 10 Gm. in a pregnant woman is at the lower limit of normal. Sternal marrow studies may give valuable information in patients with borderline counts. Whereas the normal myeloid-erythroid ratio does not run below 3 to 1, the proportion of normoblasts is higher in patients after hemorrhage or with iron deficiency.

Several years ago, I discussed before this Society a paper by Dr. Grier on acute leucemia occurring in the sixth month of pregnancy. Since then I have seen another similar case in the fourth month of pregnancy. The patient died a month and a half later. Occasionally, it is possible to keep such patients alive with blood transfusions until the fetus becomes viable. Problems come up in treating leucemia in pregnancy which never occur in the nonpregnant cases.

Another case of interest is a woman, seen in 1932, with a familial hemolytic anemia. Splenectomy was refused at that time. She became pregnant eight years later, and when seen after three months, had a rather marked anemia. Splenectomy was performed at this time without interference with the pregnancy. The blood count returned to normal and her subsequent course and delivery were uneventful.

The effect of pregnancy in stimulating myelopoiesis is brought out by another patient. For a period of six months, she had a leucocyte count of 2,500 to 3,500, with an average of 15 to 20 per cent neutrophilic granulocytes. The erythrocyte and thrombocyte counts were normal. Sternal puncture showed a slight drift to the left in the myeloid cells. Two months after becoming pregnant, the leucocyte count was 5,000, and the differential count was normal.

The last case I wish to mention is one that we have reported in the literature. A woman, six months pregnant, developed a typical catarrhal jaundice. Two weeks later the platelets disappeared from the peripheral blood and a typical purpura occurred. As the jaundice cleared up, the platelets gradually increased. She delivered seven weeks prematurely when the platelets were back to 75,000. There was no excessive bleeding during or after delivery. It has been pointed out previously that women with hemorrhagic disease get along surprisingly well during labor, though they may have trouble after delivery.

The above cases illustrate some of the hematologic problems that arise during pregnancy. A study of the sternal marrow is often of considerable help in making the diagnosis and planning treatment.

DR. WOLFF (Closing).—Dr. Schmitz questions the technique of obtaining and analyzing the bone marrow fluid. Limarzi has performed bone marrow analysis via sternal puncture as described in over 2,700 patients. The findings obtained in both health and disease are well known. We have used this method in over two hundred women during various intervals of their pregnancy. In our hands the technique seems to be simple and yields accurate results.

We have not made a thorough study of iron deficiency anemia per se. While determining the correlation of the peripheral blood and bone marrow findings in a group of

normal healthy women during pregnancy, we encountered cases of iron deficiency anemia and have reported the findings in these patients. Thus we have no statistics to present on the incidence of this type of anemia during pregnancy. However, we do feel that these iron deficiency anemias are not quite as prominent as reported by some investigators. Our patients are all of the low income clinic variety, and we do not find too many with this hypochromic anemia.

We feel that iron medication does not have any prophylactic value during pregnancy. It is only of value in the true hypochromic anemias. Iron medication itself may do harm since it often leads to nausea and other gastrointestinal disturbances.

As to routine sternal aspiration, it is necessary only in the anemic patients or those having symptoms suggestive of a blood dyscrasia. We have a rule in our clinic that when the hemoglobin is below 70 per cent, the patient is referred to the hematology department. A complete study of the peripheral blood is made. If the patient is found to be anemic, then a sternal marrow puncture is performed. It is thus a routine procedure on the anemic patients.

May I thank Dr. Alt for his kind remarks. Yes, we have found only scant reference to sternal punctures during pregnancy. We feel that this study has been neglected. We feel that both the hematologist and the obstetrician may obtain important clinical information from this study of the bone marrow.

STUDIES ON THE RED FLUORESCENT PORPHYRIN DEPOSITS ON VAGINA AND CERVIX

A Possible Aid in the Detection of Malignancy

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PORPHYRIN, in combination with iron (heme), forms the active part of such molecules as cytochrome-c, hemoglobin, peroxidase, catalase, and myoglobin.[1, 6, 15, 16] In the form of these metal complexes, they are therefore present in all cells, including bacteria, yeasts, and cells of higher animals. There are many types of porphyrin, but the most common one in tissues of the human subject is protoporphyrin-9, which is the basic nucelus of hemoglobin after iron and globin have been removed.[1, 6] The normal degradation of hemoglobin in the liver probably does not result in the formation of protoporphyrin, but the iron porphyrin ring is opened up before the iron is removed.[11] Free porphyrins are red fluorescent in near ultraviolet light. It has been previously demonstrated[4, 9] that porphyrins are frequently present on the female genitals in amounts sufficient to cause a red glow when examined in this light (Wood's) in a darkened room.

The present interest in the relation of porphyrins to gynecologic problems stems from the postulate that there may be etiologic factors preceding, and sometimes accompanying, the development of carcinoma of the cervix. The previous work which supported this hypothesis[3, 4, 9] led to the supposition that the presence of porphyrins may, on occasion, lead us to suspect a carcinomatous lesion of the uterus which would not be detected otherwise. In the present survey, we have determined the normal incidence of this red fluorescent material in its relation to the menstrual cycle. This study indicates that the presence of porphyrins cannot be used to detect early stages of cancer, to the exclusion of the other methods.

In 1942, Figge and Strong[2] observed that cancer-susceptible strains of mice maintained on a Nourishmix diet possessed red fluorescent harderian glands. The harderian glands of cancer-resistant strains of mice were not red fluorescent. This led to the hypothesis that there might be a direct or indirect relationship between these substances and the development of malignancy. Later, Figge[3] correlated this same fluorescence of the harderian gland of other animals with their relative susceptibility to spontaneous and induced tumors. The entire hypothesis and supporting data are published elsewhere.[5] In attempting to apply this hypothesis to the human subject, a search for porphyrins in cancer-susceptible organs and tissue was initiated. This led to the rediscovery of red fluorescent deposits (porphyrin) on the female genitals.[4, 9] In the previous studies on women, the greatest amounts of porphyrin, by far, appeared in foul lochia, where it was

shown that red fluorescent deposits (porphyrins) were sometimes present for a month or two. Obviously the fluorescent material would be pooled about the cervix uteri during most of this time. In nonputrid lochia, as well as in other conditions where purulent cervical discharge was abundant, red fluorescence often was absent. Frequently red fluorescence was found about the clitoris when not visible elsewhere on the genitals. It was noted also that in some women the red fluorescent deposits were found about the vulva and vagina following the menstrual flow, but not intermenstrually. The red fluorescent material was shown to contain porphyrins, which were identified by solubility and spectrographic methods.[4] It was thought that the porphyrin arose through the action of certain bacteria on blood or other cellular elements, but other possibilities were also entertained. For complete details of these studies and color photographs of the deposits on the female genitals, the reader is referred to the preceding papers.[3, 4, 9] Hauser,[8] who first noted red fluorescence of the genitals in 1929, also related these porphyrin deposits to the decomposition of blood acted upon by a specific bacterial flora.

The discovery of the porphyrin deposits on the female genitals strengthens the hypothesis which related porphyrin to the development of carcinoma, but certainly no actual proof of an etiologic relationship was found. It became clear that the incidence of porphyrin in normal women at various stages of the menstrual cycle should be determined before engaging in any further speculations or investigations concerning its role in the development of female genital cancer. Hence, the following planned investigations were carried out on a large group of women whom we considered as women menstruating normally. They were able and willing to cooperate in a planned procedure which would determine the presence of porphyrin postmenstrually and intermenstrually. The accumulated data were tabulated to indicate how often porphyrin occurs on the genitals of normal women, what factors govern its production, and of what diagnostic value are these red fluorescent deposits.*

Materials and Methods

1. A large group of volunteer women, patients with pulmonary tuberculosis, confined to a sanatorium, inserted a medium-sized open cone vaginal tampon of standard make on the evening of the last menstrual day. They removed the tampon and placed it in a container the following morning. The patient wrote her name, case number, and the date on the lid of the container. The tampon was examined under near ultraviolet light in a darkened room within three days before any significant decrease in fluorescence occurred. The patient avoided douches or vaginal wash until after a second vaginal tampon was used one week later; that tampon was similarly inspected for fluorescence. A rough quantitative scale was employed to indicate degrees of fluorescence encountered. Thus, small areas of dull fluorescence were indicated as traces; larger areas of weak fluorescence and minute areas of intense amounts of fluorescence were described as slight; intensely fluorescent material covering areas approximately 1, 2, 3, and 4 square centimeters of tampon surface were labeled respectively as plus 1, plus 2, plus 3, and plus 4. As a further indication of the range of this quantitative scale, it may be stated that tampons described as plus 1, probably contained at least fifty times as much porphyrin as those labeled "trace."

2. By the end of four calendar months, sufficient material had been collected to establish the normal incidence of porphyrin during the menstrual cycle. Following the tabulation of these data, further studies were carried out to rule out pelvic tuberculosis as a cause of porphyrin formation, for it is known that tubercle bacilli growing in culture are porphyrin producers and are red fluorescent. At the same time, an attempt was made to

*This study was accomplished by the cooperation of the patients and physicians of Olive View Sanatorium, with especial assistance by Dr. Ann Statz and Dr. Paul Smith.

determine the source of the porphyrins and to ascertain whether the porphyrins had caused any morphologic changes in the cervices of those patients who consistently produced them. In addition, porphyrin analysis was made on some of the most intensely fluorescent tampons.

Limitations of the Methods

A few of the patients could not determine accurately when the menstrual period would end, and these women, for the most part, did not submit either postmenstrual or intermenstrual tampons when they were undecided about this. However, all of the patients kept an accurate calendar of their days of bleeding and the days tampons were used, so that a good cross check against error was established.

Each woman was given instructions how to insert the tampon high in the vagina so that it would rest against the cervix and posterior fornix. Obviously the success of the placement depended somewhat on the patient's manual dexterity and enthusiasm. The exact evening the patient chose as the time menstruation had been completed also must have varied somewhat between patients and between the successive periods of menstruation of any one patient. This may account for some of the differences in degrees of fluorescence between successive examinations and between individuals, for if considerable blood is collected on a tampon, the blood may quench some of the porphyrin fluorescence. Blood itself is not fluorescent. (See Fig. 1.) Additional variations were found in the bacteriologic study and will be mentioned later.

Nearly all of these volunteer women were married, younger than average age of the general population, and about one-third were nulliparous. These factors may or may not have made a difference in the fluorescence frequency found. Most of the patients were of average intelligence and were willing and able to follow instructions extremely well. However, a few were illiterate and the accuracy of their data depended on help by other patients.

Extent of the Survey

The 172 volunteer women were somewhat younger than the age for maximum carcinoma incidence. Ninety-five were between 20 and 29 years of age; fifty-nine between 30 and 39 years of age. These two age groups accounted for 90 per cent of the volunteers. There was only one patient as old as 50 years, and the youngest was 18 years of age. Most of the women had never used vaginal tampons, but very few experienced any discomfort from their use. Most of the unmarried women were, of course, excluded. Because multiparity has an important relation to carcinoma of the cervix, it is of interest to note that 56 of the patients were nulliparous, 39, primiparous, and 74, multiparous. As will be noted later, this difference seemed to have no bearing on the presence or absence of red fluorescent material. The analysis of the data collected will be summarized under three headings: i.e. (a) postmenstrual fluorescence, (b) intermenstrual fluorescence, and (c) the cause and effects of persistent intense fluorescence. The part of the investigation involving the use, collection, and examination of tampons covered a period of 4 calendar months. During that time 753 tampons were examined for fluorescence—413 postmenstrual and 340 intermenstrual.

Results

Postmenstrual fluorescence.—Postmenstrual tampons frequently showed areas of intense fluorescence (Fig. 1, *d*), hence it seems more advisable to indicate the number of women showing definite quantitative amounts at any time during the study, rather than to indicate the number of times any particular quantity was found on the tampons. Another reason for summary of persons rather than tampons, is that there was variation in the quantities recovered from any one person from month to month. Often the quantitative fluctuation was not great, but not infrequently it was. Some of the reasons for these differences have been enumerated under the heading "Limitation of Methods." Other factors, such as variation in the amount of menstrual flow, and changes in bacterial flora, will be discussed later. The true quantitative incidence is probably in the region of that found as the greatest amount on any one examination rather than the average amounts found on several

examinations, because the interfering factors will all tend to lower the observed quantitative amount. For example, there were only 36 women whose postmenstrual tampons *averaged* plus 1 or greater, but 65 volunteers (38 per cent) submitted at least one tampon which had an area of intense red fluorescence classified as plus 1 or greater; thus 102 (62 per cent) submitted tampons which showed only slight amounts or none at all. Those exhibiting fluorescence in 3 plus or 4 plus amounts (Fig. 1, *d*) probably comprise about 10 per cent of the population, for the total number exhibiting fluorescent material in these amounts during the course of study was 13. Table I will give a somewhat more detailed report of those exhibiting fairly intense fluorescence, and Fig. 1 illustrates a tampon with blood (a), and no fluorescence (b); another with some blood and much porphyrin (c), and fluorescence of plus 3 intensity (d). Briefly, the results of postmenstrual specimens may be summarized as follows: a quantity of porphyrins sufficient to saturate the surface and produce intense red fluorescence of vaginal tampons under near ultraviolet light was present postmenstrually in approximately 10 per cent of the women studied, and lesser amounts, but still sufficient to cause intense fluorescence, were found in about 40 per cent of the women. The tampons of about 60 per cent of the women studied do not exhibit more than slight amounts of red fluorescent material or none at all.

TABLE I. FLUORESCENCE OF POSTMENSTRUAL TAMPONS

GROUP	FLUORESCENCE OF POSTMENSTRUAL TAMPONS	TOTAL NO. INDIVIDUALS
(1)	0 → 2	8
(2)	1 → 2 0 → 3	13
(3)	1 → 3 2	4
(4)	1 → 4 2 → 4 2 → 3	5
(5)	4	1
	Total	31

Intermenstrual fluorescence.—In order to determine whether porphyrin is present intermenstrually, the patients inserted a second tampon one week after the first tampon had been used. This second tampon not only demonstrated whether porphyrins were present through the entire menstrual cycle, but also determined whether the intermenstrual bleeding, which is frequently found at this time, will cause intense fluorescence. Rutherford[13] found that whereas the average appearance of intermenstrual bleeding was on the 17.6 day of the cycle, microscopic bleeding was occasionally found from the fourth to the twenty-third day of the cycle. Hence, the time we chose enabled us to determine fluorescence when no normal uterine bleeding was occurring, and at the same time probably gave us a good sampling of cycles in which microscopic bleeding occurred.*

Most of the tampons collected at this time and examined under near ultraviolet light failed to show red fluorescence. This was true even when the postmenstrual tampon from the same patient had shown intense red fluorescence. However, traces or faint fluorescence was noted on 33 tampons (10 per cent, so was frequent enough to be considered a usual

*77 per cent of the patients' periods lasted 3 to 5 days, and 18 per cent 2 or 6 days, therefore, 95 per cent of the tampons were used following ninth to thirteenth day of the menstrual cycle.

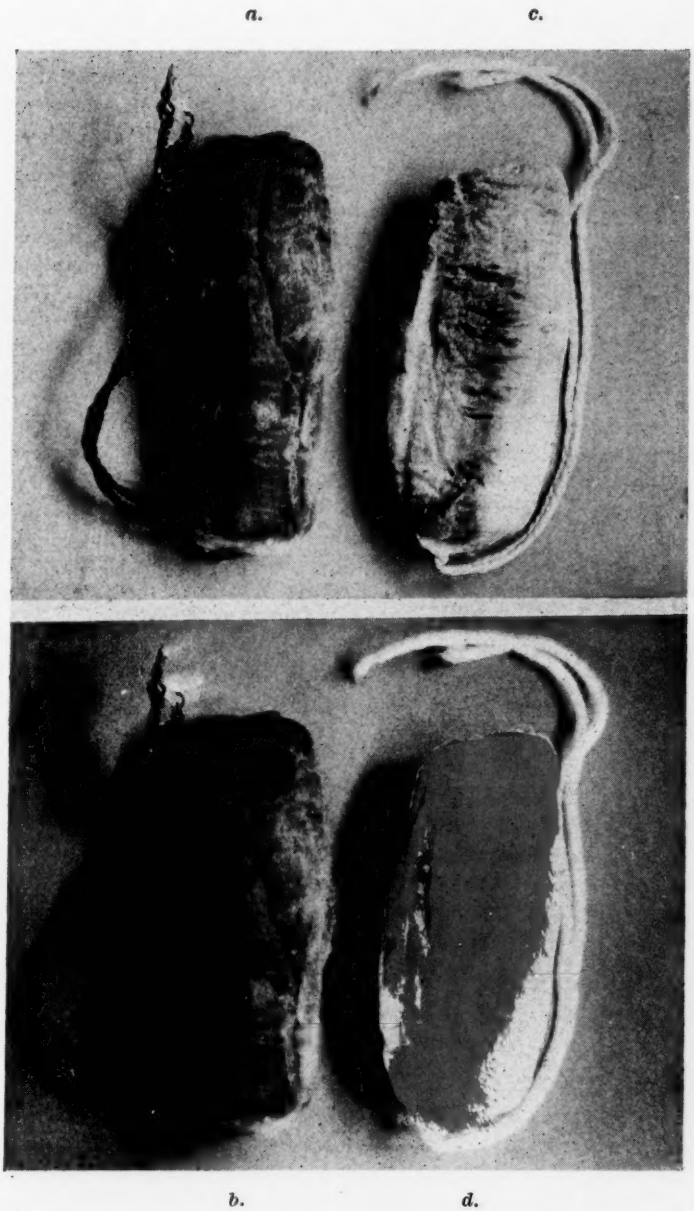

Fig. 1.—Representation in Ben Day Process of the contrast recorded on Kodachrome film between two vaginal tampons, one containing blood and no porphyrin, the other slight blood and much porphyrin.

Tampon I: Artificially treated in blood. *a*, In ordinary light this appeared red; *b*, in near ultraviolet light it appeared entirely black in conformity with the fact that blood does not fluoresce.

Tampon II: *c*, Brown stained, postmenstrual tampon in ordinary light. *d*, When illuminated with near ultraviolet light the stained areas fluoresced a brilliant red.

phenomenon). An association with intermenstrual bleeding is probable, but was not established. In addition to these tampons with pale fluorescence, there were four tampons classified as slight fluorescence, two classified as plus 1, and one identified as plus 3. One patient who submitted a plus 1 tampon left the hospital before further investigation was possible, but four of the volunteers who submitted these more intensely red fluorescent tampons were given special examinations. The data obtained are summarized below:

CASE 1.—D. D. Aged 50 years. Para iv. One intermenstrual tampon: fluorescence plus 3. Other intermenstrual tampon: 0 fluorescence. Postmenstrual tampon: slight or 0 fluorescence. This patient denied bleeding in the interval between the postmenstrual and intermenstrual tampons, but said there was bleeding for 3 days after the second tampon was used. She denied any previous intermenstrual bleeding. Pelvic examination: no pelvic abnormality except slight chronic cervicitis. Cervix biopsied: chronic inflammation and some hypertrophic changes in the cells of one endocervical gland. Repeat intermenstrual tampon two months later: 0 fluorescence. Impression: Metrorrhagia. Fluorescence probably related to imperceptible endometrial flow. Advise: Curettage if further metrorrhagia.

CASE 2.—R. S. Aged 38 years. Para i. One intermenstrual tampon: fluorescence, slight. Other intermenstrual tampon: 0 fluorescence. Postmenstrual tampon: fluorescence, slight or 0. Patient denied any intermenstrual bleeding, but stated that menstruation was scanty and prolonged, and she found it difficult to determine when menstruation ended. The postmenstrual tampon one week before had been saturated with blood. Impression: Fluorescence might be associated with imperceptible endometrial flow continuing several days after the first tampon was used.

CASE 3.—R. B. Aged 46 years. Para i. One intermenstrual tampon: fluorescence, slight. Other intermenstrual tampons: fluorescence, 0. Postmenstrual tampons: all showed intense fluorescence. This is one of the patients of special study, Table I. Pelvic examination: chronic hypertrophied cervix, uterine descensus, cystocele, rectocele. History of irregular and profuse menstruation. Cervix biopsied. Advise: Operation. Impression: Fluorescence probably related to imperceptible uterine flow.

CASE 4.—E. O. Aged 24 years. Para ii. One intermenstrual tampon: fluorescence, slight. Other intermenstrual tampons: fluorescence, 0. Postmenstrual tampons: all showed intense fluorescence. This is one of the patients of special study, Table I. Pelvic examination: no pathologic condition. Patient denied intermenstrual bleeding or irregular periods. Impression: Intermenstrual fluorescence not explained, but may be related to the regular intense postmenstrual fluorescence.

CASE 5.—A. H. Aged 22 years. Para i. Intermenstrual tampon: fluorescence, slight. Other intermenstrual tampons: fluorescence, 0. Postmenstrual tampons: fluorescence, 0 or slight. Patient denied any intermenstrual bleeding or irregularity of periods. Not examined. Impression: intermenstrual fluorescence not explained.

CASE 6.—C. O. Aged 21 years. Para i. One intermenstrual tampon: fluorescence, plus 1. Other postmenstrual tampons: plus 1, 0, 0. Periods at about 6-week intervals, lasting 5 days, but it was difficult for patient to remember dates. Denied intermenstrual bleeding. Patient not examined. Impression: intermenstrual fluorescence not explained.

CASE 7.—M. L. Aged 29 years. Para 0. One intermenstrual tampon: fluorescence, plus 1; other intermenstrual tampons: trace. Postmenstrual: plus 1 and plus 2 fluorescence. Patient left the hospital before examination was possible.

To summarize the study of these seven women: three of these patients gave evidence of possible abnormal uterine intermenstrual flow. Two others showed persistent intensely fluorescent postmenstrual tampons, and one could not be followed for further study. Three others gave no history of menstrual

irregularity, but only one of these could be examined. Because we have seen intense fluorescence intermenstrually in cancer of the uterus, we feel that the above normal incidence of moderate intermenstrual fluorescence (about 1 per cent) to be so low, that we can state, for diagnostic purposes, that *intense fluorescence intermenstrually (of the order of plus 2 or greater) should be considered an evidence of abnormal uterine flow probably associated with imperceptible bleeding which demands further study, such as curettage and biopsy of the cervix, and hence demands as much attention as visible metrorrhagia.*

In conclusion, intermenstrually, traces of red fluorescent material were present in 10 per cent of the cases and cannot be considered too unusual. However, more intense fluorescence at this time is rare. Small amounts of intense fluorescence which could not be explained were found in about 1 per cent of a series of 340 intermenstrual tampons. Therefore, it seems safe to assume that larger amounts of intense fluorescence intermenstrually are also rare.

The cause and effects of persistent intense fluorescence.—It has been shown above that intensely fluorescent intermenstrual deposits occurred in only 1 per cent of the women, whereas intensely fluorescent postmenstrual deposits occurred regularly following each menstrual period in about 10 per cent of the women. Because of the previous postulates that porphyrin is in some manner related to the development of carcinoma, this intermittent, and regular occurrence of porphyrin deposits about the cervix in some women and not in others, necessitated further study of some of these patients.

An attempt was made to determine, first, why these porphyrin deposits occurred in some women and not in others; and second, to find out whether any gross microscopic pelvic abnormalities could be discovered in porphyrin producing patients. Since the patients submitting tampons were volunteers, it was impossible to carry out extensive studies on all of the women. It was possible, however, to do a pelvic examination, culture the cervical secretion, test for pH of these secretions, and biopsy the cervix of ten women showing regular intense fluorescence and examine eleven women (as controls) whose tampons failed to show fluorescence during the months this study was conducted.

Tabulation of some of the findings of these twenty-one women may be found in Table II. In choosing the controls, many multipara were selected, for carcinoma of the cervix is about 8 or 9 times as frequent in the multiparous women as in the nulliparous.[7, 12]

Any histologic effects produced by parity should be present in the controls as well as in those showing intense fluorescence. The pelvic examinations were carried out on a stretcher or flat table to facilitate complete exposure of the cervix in all of the speculum examinations; the cervical biopsies were taken with a punch biopsy forceps.

Since porphyrin producing bacteria are said to thrive and produce porphyrin only in alkaline media,[10] it was necessary to test the cervical secretions for acidity. Nitrazine paper was used for this determination, but, as might be expected from the fact that the endocervical secretions are alkaline and the vaginal usually acid, some determinations lay on the alkaline side and some on the acid side, but there was no correlation of this with fluorescence. Because it was impossible to examine the patients without using some lubricating jelly, and in addition, because the culture media differed so widely from the vaginal secretions, the results we obtained from culture of the cervix were highly inadequate and only suggestive of the actual flora present. Cultures were plated on glucose blood agar, at reduced oxygen tension and under atmospheric conditions, and on Wallenstein's media.

Chromogenic and fluorescent colonies grew more frequently on the Wallenstein's media which is rich in egg and hence is a high porphyrin media. However, when some fluorescent *Escherichia coli* colonies were taken from this media or the glucose blood agar media, and then planted on plain agar or plain blood agar, or eosin methylin blue media, they

TABLE

NO.	NAME	TAMPONS BEFORE	AGE USED	TIMES PREGNANT	POSTMENSTRUAL FLUORESCENCE	INTERMENSTRUAL FLUORESCENCE
1	M. A.	No	25	4	2, 1	0
2	W. A.	Yes	22	1	3	0, 0
3	E. P.	Yes	34	0	2, 4, 3, 2	0, 0, 0
4	M. M.	No	36	1	3, 1, 0	Tr., 0
5	W. F.	No	24	2	3, 4	–
6	R. B.	No	46	1	4, 1, 2	Tr., Tr., Sl.
7	E. D.	No	46	3	1, 3	0
8	A. B.	Yes	20	0	2, 2	Tr., 0
9	E. M.	No	20	1	2, 2, 1	0, 0, 0
10	E. O.	No	24	2	4, 2, 1	Sl., 0, 0
1	K. G.	No	31	2	0, 0, 0, 0	0, 0, 0, 0
2	E. K.	No	25	2	0, 0	0, 0
3	A. G.	No	30	0	0, 0, 0, 0	0, 0,
4	E. F.	No	43	1	0, 0, 0	0, 0, 0
5	R. C.	No	37	2	0, 0,	0, 0
6	M. D.	Yes	29	1	0, 0, 0	0, 0, 0
7	C. R.	No	24	2	0, 0, 0	0, 0, 0
8	N. E.	No	34	11	Tr., 0, 0,	0, 0, 0
9	R. R.	No	34	3	0, 0, 0	0, 0
10	C. A.	No	36	11	0, 0	0
11	C. V.	No	36	6	0, 0	0, 0, 0

lost their fluorescence. Furthermore, it was shown that coli colonies nonfluorescent on plain agar acquired a red fluorescence when grown on Salmonella Shigella media and then again lost this fluorescence when replated on plain agar. Although this red fluorescent-acquired property from Salmonella Shigella agar media probably was not due to porphyrin, it served as a good illustration of how important the media might be in the production of fluorescence by bacteria. The media used did not duplicate well the natural media of the vagina, but fluorescent bacterial colonies did appear occasionally on the media we used. These colonies were usually one

II

EXAMINATION	CULTURE	BIOPSY
Slight eversion of cervix.	2 slightly fluorescent colonies: Actinomyces.	Many surface neutrophiles. Slight cell infiltration of stroma.
Eversion and slight chronic cervicitis.	No fluorescent colonies.	Wide cornification.
Cervix healthy (patient says she has a foul discharge 5 days after period ends).	Many fluorescent colonies: coli.	Narrow zone of round cell infiltration below squamous epithelium.
Cervix healthy.	No fluorescent colonies.	Squamous epithelium normal. No stroma present.
Chronic cervicitis.	2 tiny intensely fluorescent colonies: Staph.	Wide cornification.
Chronic hypertrophied cervix; cystocele; rectocele; uterine descensus (irreg. and profuse menstrual periods).	No fluorescent colonies.	Moderate squamous metaplasia.
Cervix healthy (was cauterized several years ago).	Very slight fluorescence of a few colonies.	Very slight squamous metaplasia.
Cervix healthy.	Many fluorescent colonies: Staph.	Squamous epithelium normal. (No stroma.)
Cervix healthy (periods last only one day).	One moderately fluorescent colony.	Extreme infiltration with neutrophiles; epithelium greatly thickened. Only slight cornification.
Cervix healthy.	Few intensely fluorescent colonies: Strep.	Squamous epithelium normal.
Cervix healthy.	No fluorescent colonies.	Neutrophiles on surface; extensive metaplasia. Wide cornification.
Cervix healthy.	1 small intensely fluorescent colony: Staph.	Wide cornification; moderate squamous metaplasia.
Much endocervical mucus.	Very faint fluorescent of few colonies.	Moderate round cell infiltration.
Few Nabothian cysts.	No fluorescent colonies.	Moderate round cell infiltration of endocervix.
Eversion of cervix and chronic cervicitis.	No fluorescent colonies.	Endocervical glands greatly dilated. Squamous epithelium normal.
Slight chronic cervicitis and Nabothian cysts.	No fluorescent colonies.	Extensive squamous metaplasia.
Cervix healthy.	Few slight fluorescent colonies (fade in 2 days): coli.	Slight squamous metaplasia.
Slight chronic cervicitis and Nabothian cysts.	Many fluorescent colonies (fade in 2 days): coli and diphtheroids.	Normal squamous epithelium.
Very slight chronic cervicitis.	No fluorescent colonies.	Slight endocervical round cell infiltration. Squamous epithelium normal.
Subacute cervicitis with a slight bleeding on examination.	No fluorescent colonies.	Tubercles, round cells and neutrophiles. Acid fast stain: tubercle bacilli.
Slight hypertrophy and chronic cervicitis. Moderate eversion.	No fluorescent colonies.	Extensive round cell infiltration of the endocervix.

specific strain of bacteria in a given individual, but several different bacteria (as shown in Table II) were isolated from the group of patients.* Furthermore, the tubercle bacilli were not grown in culture from any of the women. It may be well to point out again that in Stander's Clinic[14] at the New York Hospital, the common organisms cultured from foul lochia were found to be principally anaerobic streptococci, staphylococci, and occasionally coli and diphtheroids. In the previous papers it was shown that there are large

*Dr. H. E. Pearson assisted in identifying the bacterial colonies.

amounts of porphyrin present in foul lochia, and the organisms found in this study which were productive of red fluorescence apparently are similar organisms.

The biopsies of the cervices failed to show any change which definitely could be related to porphyrin. One woman exhibiting fluorescence did show a highly proliferative squamous epithelium, but this might be caused by infection alone; furthermore, it was not a malignant lesion. One other biopsy specimen showed tuberculosis, but this was from one of the control patients.

The identity of the porphyrins extracted from the vaginal tampons.—The fluorescent portions of tampons were removed and combined because extraction of a single tampon was not practical. The method of extraction was the same as that used previously for the extraction of lochia pads.[4] The absorption bands in 25 per cent HCl were determined by means of a Beckman Quartz Spectrophotometer. These were compared with the bands noted by other investigators and the absorption bands of synthetic porphyrins. The HCl numbers and absorption bands listed in Table III indicate that three porphyrins (coproporphyrin, deuteroporphyrin, and protoporphyrin) were extracted from the tampons. These are the same as those isolated from lochia pads. However, the absorption bands at the 0.6 per cent HCl fraction in the violet end of the spectrum indicated that this was mainly deuteroporphyrin and that little, if any, mesoporphyrin was present. Since all of these three porphyrins may be derived from protoporphyrin, they probably arose from the degradation of hemoglobin or some other heme containing cell substance.

TABLE III. ABSORPTION BANDS AND HCL NUMBERS OF PORPHYRINS EXTRACTED FROM VAGINAL TAMPONS

SOURCE OR TYPE OF PORPHYRIN	PER CENT HCL USED TO EXTRACT FROM ETHER	MAIN ABSORPTION BANDS MILLIMICROMS SOLVENT 25 PER CENT HCL			DIAGNOSIS
Tampon	0.10	592.0	550.0	405.0	Coproporphyrin
Tampon	0.60	590.0	550.0	404.0	Deuteroporphyrin
Tampon	2.00	618.0	556.0	410.0	Protoporphyrin
Coproporphyrin F.*	0.08	592.2	548.7		
Coproporphyrin S.*	0.09	593.9	550.2	405.8	
Deuteroporphyrin S.	0.40	591.0	548.0	404.0	
Mesoporphyrin F.	0.50	593.1	550.7	508.7	
Protoporphyrin F.	2.00	602.4	557.2		
Protoporphyrin S.		602.7	557.2	410.8	

*Values of Fischer and Schumm.

Discussion

The previous papers have discussed adequately the hypotheses relating cancer to porphyrin sensitization and have correlated the findings with these postulates.[2, 4, 5, 9] There are two main questions which should be answered, i.e.: (1) are porphyrins a causative factor in the development of carcinoma of the uterus? (2) can the presence of red fluorescence be used as an aid in the diagnosis of malignancy of the uterus? The present observations as they relate to these two problems form the basis for the discussion which follows.

1. *Are porphyrins a causative factor in the development of malignancy?*—In the present study we have not been able to show that porphyrins are related to malignancy. This, however, does not mean that the porphyrin hypothesis has been disproved, for the proof of a definite relation to malignancy may be a very difficult endeavor. For example, the only two known factors that seem to be definitely related to carcinoma of the cervix are chronic infection and multiparity. The latter factor may be largely due to an estrogen effect, but there is no proof of this. In the present control series of the women

not showing fluorescence, these two factors were present, but there was no evidence of malignant change in these women either. In fact, most women subjected to these two factors do not develop carcinoma of the cervix, and in a group of women in this age distribution several thousand might be examined without finding evidence of malignant change. So, too, in proving an etiologic relationship of porphyrin to cancer, equally large series of women examined over a long period of time would be necessary for proof or disproof of this hypothesis. This is a much larger project than we have been able to carry out. The proof or disproof may be more easily accomplished by means of animal experimentation. (This is being attempted at the present time.) On the other hand, some of the findings of the present survey fit in with what we know should be required of a causative agent in the development of malignancy. From animal work with carcinogenic agents we know that their intermittent application over a long period of time may be more successful in producing tumors than a continuous application, or a short intense application. Furthermore, we know that all animals subjected to large amounts of carcinogens do not develop tumors, but it is a combination of several factors which results in malignancy. The fluorescent material found to occur postmenstrually is present in appreciable amounts in about 40 per cent of women (this is less than the incidence of either multiparity or chronic cervical infection) and in more intense amounts after every menstrual period in only about 10 per cent of women. Furthermore, it is apparent that this substance occurs intermittently over a number of years, and during the years when cancer incidence of the cervix is greatest. Moreover, it has been shown previously[9] that additional, larger amounts may occur in postpartum women who have developed foul lochia; here the porphyrins could be agents which are synergistic with both the factor of chronic infection and parity.

2. *Can the presence of red fluorescence be used as an aid in the diagnosis of malignancy?*—In the study of postmenstrual tampons, we showed that large amounts of intensely fluorescent deposits may occur immediately following the menstrual period. Therefore, the presence of intense fluorescence at this time is not rare, and likewise cannot be used as a diagnostic aid. The biopsy of the cervix of these women showing intense fluorescence is not indicated by the presence of fluorescence alone, for we have seen that fluorescence is no indication that malignant change has been produced. Furthermore, the intermenstrual tampons demonstrated that small amounts of porphyrin may be present at this time too in 10 per cent of women. However, unexplained intense fluorescence intermenstrually is indeed rare (about 1 per cent), so that intense fluorescence at this time may be regarded as an abnormal condition and indicative of unusual uterine flow and should be regarded with as much concern as metrorrhagia. Large amounts of this red fluorescent material are sometimes found following endometrial flow, such as following menstrual bleeding, invariably found in foul lochia, and often, but not always, found in the drainage from carcinomas of the uterus.

Hence, in conclusion, we may say that if this material is present in large amounts intermenstrually it may be used as a diagnostic aid in the detection

of malignancy or any of the other causes of uterine flow. It should be emphasized, however, that early visible carcinomas of the cervix may not show porphyrin deposits, therefore, the presence or absence of porphyrins cannot be used as a test to rule out cancer. If fluorescence is to be used as a diagnostic tool, it should be used to supplement the procedures now recognized as essential, i.e., examination, biopsy, and curettage.

It is of equal importance to emphasize that no matter how small the amount of secretion in the vagina, and no matter of what color the secretions may be in ordinary light, they still may contain large amounts of intensely fluorescent material when exposed in near ultraviolet light alone, and when these porphyrins are present, the secretions are most certainly not just simple vaginal secretions. Porphyrins when present in large amounts in the vagina in the postmenopausal woman, or intermenstrually one or two weeks following the use of a vaginal tampon or postmenstrual cleansing douche in the woman still having her periods (when the examination is made one or two weeks following the use of a vaginal tampon or postmenstrual cleansing douche) should be regarded as a sign of abnormal uterine drainage and is an indication for further study to rule out malignancy. Simple lubricants which have been used in the examination will not interfere appreciably with the test. All that is required for the examination is a pledget of cotton large enough to absorb all of the vaginal secretions. After the vagina has been swabbed with this, the cotton pledget may be placed immediately (or after some hours) under the standard "black lamp" which can be kept in either a dark corner of the examining room or in a darkened room, and when this procedure is carried out the swab will instantaneously exhibit a brilliant red glow if much porphyrin is present. The test for red fluorescence (porphyrin) is thus simple, dramatic, and can easily be made an adjunct to the routine pelvic examination.

Summary

A study has been made of normally menstruating women to determine the frequence of red fluorescent (porphyrin) deposits at different phases of the menstrual cycle.

It was found that 10 per cent of the women studied showed large amounts of this red fluorescent material immediately following each menstrual period, about 28 per cent more showed fairly large amounts following one menstrual period, but not after every menstrual period, while 62 per cent of the women showed only traces or no porphyrin postmenstrually.

Culture from a swab of the cervix of some of these women showed porphyrin producing organisms of staphylococci, streptococci, actinomyces, diphtheroids, and coli. Biopsy of the cervix of a representative group of these showing red fluorescence and a control group of others not showing fluorescence, failed to demonstrate any evidence of microscopic change produced by this material.

A survey of red fluorescent deposits intermenstrually revealed that traces of red fluorescent material in the vagina are not uncommon at this interval, but intensely red fluorescent secretions are rare enough to be regarded as

abnormal. The latter finding may possibly prove to be a diagnostic aid in the detection of abnormal uterine flow, not associated with gross bleeding and the limitations and possibilities of this test are outlined. The test for this red fluorescent material is simple and dramatic, and it requires no special apparatus to determine its presence other than a standard "black lamp outfit." The test is not a substitute for examination, biopsy, curettage, or any of the tests now in use for the detection of malignancy, but may be used as an adjunct to present methods, and should aid in focusing attention on the problem of carcinoma of the uterus.

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STUDIES ON HIGH DOSAGE PROGESTERONE THERAPY OF AMENORRHEA*

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IT HAS been demonstrated by Zondek[1, 2] that bleeding can be rapidly induced in many women with functional amenorrhea by the administration of progesterone in high dosage over a period of several days. If primary amenorrhea is present or if the secondary amenorrhea is of long duration, it is necessary to prime the uterus first with estrogen or to administer estrogen with the progesterone. Zondek and his associates have shown that progesterone withdrawal bleeding can occur from an endometrium which shows only a slight proliferative effect.[3, 4] It can be induced soon after a normal menstrual period, but not during the normal corpus luteum phase or during pregnancy.[1] Zondek's method of treatment of amenorrhea is being widely employed because it is rapid and obviates the use of large dosages of estrogens over a long period of time with possible inhibitory effect on the anterior pituitary.

It is probable that the initial bleeding after the administration of progesterone results from the direct effect of the hormone on the endometrium. However, that progesterone may have a more important effect on the sex-endocrine mechanism is indicated by the fact that in some of the patients one or more spontaneous bleedings will occur following the discontinuation of treatment, and during this interval it is occasionally possible for a pregnancy to occur.[1] It is these latter observations which add considerable weight to the importance of high dosage progesterone therapy and indicate the desirability of further investigation of the underlying endocrine mechanism.

To shed further light on various phases of this problem, we carried out the following types of clinical investigation:

1. An evaluation was made of the endocrine status of the amenorrheic patients to be treated. In addition to clinical observations, hormone assays for estrogens, gonadotrophins and 17-ketosteroids were made by methods previously published from our laboratory.[5] Vaginal smears for cytologic study were also taken, and in selected cases endometrial biopsies were obtained.

2. High dosage progesterone alone was the initial treatment given to these patients in almost all instances. Generally, this therapy consisted of the intramuscular injection of 20 mg. of progesterone on each of three consecutive days. When this type of treatment failed, the patients were primed with small amounts of estrogens orally for one to two weeks, and then the progesterone was repeated. Occasionally, the estrogen was given in high dosage by injec-

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tion along with the progesterone as recommended by Zondek;[2] usually we gave 10,000 rat units of alpha-estradiol benzoate and 20 mg. of progesterone at each injection.*

3. In selected cases, hormonal assays and endometrial biopsy were repeated during the course of treatment and at intervals following therapy. Vaginal smears were made frequently on all cases.

The pertinent clinical data of the amenorrhea cases studied are summarized in Tables I, II, and III.

TABLE I. PATIENTS STUDIED

Number of patients	51
Age range	18-36
	18-25=34 patients
	26-36=17 patients
Marital status	
Single	21
Married	30
Fertility	
Primary sterility problem	20
1 child sterility	2
Undetermined	8

TABLE II. TYPE OF AMENORRHEA AND DURATION

Primary	7
Secondary	44
Duration of Secondary Amenorrhea	
More than 2 years	
2 to 13 years	19
1 to 2 years	5
6 months to 1 year	14
Less than 6 months	6

TABLE III. ENDOCRINE STATUS

	PRIMARY AMENORRHEA	SECONDARY AMENORRHEA	TOTAL
Gonadotropic deficiency	2	16	18
Primary ovarian deficiency	4	24	28
Adrenogenital syndrome		4	4
Endometrial defect	1		1

Primary Amenorrhea

There were 7 patients with primary amenorrhea (Table IV) varying in age from 18 to 25.

Gonadotropic Deficiency.—In two of these cases there was a gonadotropic deficiency as indicated by absence of gonadotropic hormone in the urine and diminished estrogens. In neither of these cases was it possible to induce bleeding by the cyclic administration for three months of pituitary gonadotrophins or a combination of pituitary and chorionic gonadotrophins (Synapoidin). In one of these patients the gonadotrophin was followed by 20 mg. of progesterone on three successive days without effect. These observations suggest that in these patients the ovaries may be incapable of stimulation by gonadotrophins. Cyclic bleeding was finally induced in one of these patients by priming with

*The following hormones were supplied through the courtesy of Dr. Max Gilbert of the Schering Corporation, Bloomfield, New Jersey: ampoules of Progynon-B (alpha-estradiol benzoate), ampoules of Proluton (Progesterone), tablets of Pranone (anhydro-hydroxy-progesterone and tablets of Estinyl (ethinyl-estradiol).

TABLE IV. PRIMARY AMENORRHEA

	GONADOTROPIC DEFICIENCY	PRIMARY OVARIAN DEFICIENCY	UTERINE DEFECT	TOTAL
Number of patients	2	4	1	7
Bleeding after progesterone alone	0	0	0	0
Bleeding after estrogen and progesterone	1 1 not treated	4	0	5 of 6 treated
Subsequent spontaneous bleeding	0	1	0	1
Had 3 or more spontaneous cycles	0	0	0	0
Became pregnant	0 (neither married)	0 (one married)	0	0

estrogen and following with 60 mg. of progesterone. Either estrogen or progesterone alone failed to produce a result, nor was it possible to successfully reduce the progesterone to less than 20 mg. (10 mg. on successive days); furthermore, after a number of bleedings had been successfully induced, the ovaries still remained refractory to further gonadotropic stimulation. Hormone assays made at intervals after treatment failed to show gonadotrophins and estrogens in the urine. The second of these patients also failed to respond to progesterone in full dosage and has not yet been given the combined therapy.

Primary Ovarian Deficiency.—Four of the patients with primary amenorrhea proved on hormone assays to have a primary ovarian deficiency as indicated by excessively high gonadotrophin excretion with diminished estrogens.

Two of these patients presented distinctly eunuchoid features:

G. A., aged 24 years, had failed to bleed when treated at various times previously with estrogen or after one course of low dosage x-ray to pituitary and ovaries. The first menses was induced by priming with 0.5 mg. of stilbestrol for two weeks and following with injections of 20 mg. of progesterone on three days. This was successfully repeated on several occasions, but failed whenever the progesterone was reduced to less than 20 mg. (10 mg. twice). Sixty mg. of progesterone given without estrogen priming also failed. Although full development of the secondary sex characters occurred during the course of treatment, there was no improvement in subsequent hormone assays. The uterus remained infantile, and no endometrium could be obtained by biopsy.

G. H., aged 19 years, failed to bleed after 60 mg. of progesterone (20 mg. on three successive days) but had a good flow when this dosage was preceded by priming with 0.1 mg. of ethinyl estradiol daily for three weeks. After four such courses, similar bleeding was induced by substituting for the injections of progesterone, oral administration of 100 mg. of anhydro-hydroxy-progesterone daily for three days. This was followed by one spontaneous period without any therapy. During this month moderate amounts of both gonadotrophins and estrogens were present in the urine on two assays. The following month, the patient reverted to amenorrhea with progressive diminution in gonadotrophin and estrogen. Subsequently, it was possible to induce bleeding with 60 mg. of progesterone alone but not with 300 mg. of the oral preparation.

Two patients in this group were typical examples of the syndrome described by Varney and co-workers,[6] and Albright and associates.[7] These were of short stature, had sexual infantilism, and high gonadotrophins.

B. G., aged 23 years, had been treated previously with pregnant mare serum gonadotrophins without success. Injections of 60 mg. of progesterone over three days failed to produce bleeding. Initial priming with 0.5 mg. of stilbestrol for three weeks, followed by progesterone in the same dosage, resulted in a good flow. The progesterone was then successfully given alone in the same dosage, and then gradually reduced each month. Bleeding could not be induced when the progesterone was lowered to less than 20 mg. given in one or two injections. A total of 24 bleedings were induced. No spontaneous menses

occurred. The only hormonal change noted was a moderate reduction in the gonadotrophin titer in the cycles following progesterone administration. During the course of treatment sexual maturation occurred, but the small uterus did not grow appreciably.

H. B., aged 19 years. The first menses was induced by priming with stilbestrol for two weeks followed by 6 mg. of progesterone. Attempts to produce bleeding with the progesterone alone were unsuccessful, although it was possible to later induce bleeding with 60 mg. of progesterone after three periods had been induced with combined therapy. On one occasion the patient spotted spontaneously, but has shown no tendency to continue to cycle without treatment. There was a rapid development in secondary sex characters during the course of treatment. There was no improvement in the hormonal picture, the gonadotrophins remaining high and the estrogens nondemonstrable.

There was one patient with normal sexual development but diminished estrogens and moderately high gonadotrophins. This patient, R. A., aged 18 years, also failed to bleed after full dosage of progesterone (60 mg.), but did respond after estrogen priming. Eventually, bleeding could be induced by 10 mg. of progesterone alone, but no spontaneous flow occurred. On several occasions during treatment with progesterone alone, low normal estrogen values were obtained in the urine and by vaginal smear.

Uterine Defect.—One patient had primary amenorrhea due to a primary endometrial defect. L. B., aged 25 years, had well-developed secondary sexual characteristics, but an extremely infantile uterus since she was 13 years of age. Preliminary hormone assays showed normal titers of estrogens and gonadotrophins in the urine which appeared to show cyclic fluctuations.

Progesterone in a dosage of 60 mg. failed to induce bleeding. Preliminary priming with stilbestrol followed by progesterone also failed on four occasions to induce bleeding, even when the stilbestrol was given in a dosage of 2 mg. daily for 6 weeks before progesterone. Curettage showed a minute uterine cavity with just a small bit of polypoid tissue which, on histologic examination, showed a few atrophic endometrial glands. The vaginal biopsy taken at the same time also showed atrophic changes indicating the defect probably involved other Müllerian derivatives. On endometrial biopsy after administration of high dosage of estrogen, no tissue could be obtained.

Secondary Amenorrhea

There were a total of 44 patients with secondary amenorrhea. Results of treatment will be discussed both with regard to the duration of the amenorrhea and the type of endocrine defect.

Diminished Gonadotrophins (Table V).—

Secondary amenorrhea for more than 2 years: There were 7 patients in this group. It was possible to induce initial bleeding with progesterone alone (20 mg. by injection for 3 days) in only two of these patients. After inducing several bleedings with gradually

TABLE V. SECONDARY AMENORRHEA

	GONADOTROPIC DEFICIENCY		
	MORE THAN 2 YEARS	LESS THAN 2 YEARS	TOTAL
Number of patients	7	9	16
Bleeding after progesterone alone	2	8*	10
Failed with progesterone alone	5	1	6
Subsequent spontaneous bleeding	2	6	8
Had 3 or more spontaneous cycles	2	3	5
Became pregnant	1	0	1
Bleeding after estrogen priming + progesterone	5	1	6
Failed with estrogen priming + progesterone	0	0	0
Subsequent spontaneous bleeding	2	1	3
Had 3 or more spontaneous cycles	2	1	3
Became pregnant	1 (miscarried)	0	1

*Two treated unsuccessfully with 300 mg. anhydro-hydroxy-progesterone orally over 3 days.

reduced dosages of progesterone, both patients began to have spontaneous flows and one patient became pregnant.

M. V., aged 27 years, had been under treatment in our sterility clinic for ten years because of secondary amenorrhea and sterility. The gonadotrophins were consistently absent in the urine, estrogens diminished, and the endometrium atrophic. Treatment with low dosage x-ray to pituitary and ovaries had induced occasional periods after the first two courses of treatment, but later no response was obtained. The patient had responded to various gonadotrophins for short periods and then became refractory. After a period of amenorrhea of two years, bleeding was induced with 60 mg. of progesterone. After four periods had been induced, the patient had three spontaneous flows and then became pregnant. Estrogen and progesterone therapy were continued throughout pregnancy[8] and she was delivered of a full-term, normal baby.

All of the 5 additional patients menstruated after preliminary priming with estrogen followed by progesterone. Two of the patients menstruated spontaneously for more than 6 months after several bleedings had been induced with subsequent injections of progesterone alone, and one patient became pregnant during this interval, but miscarried at 3 months. Two additional patients had induced bleeding with progesterone alone even in dosages of 20 mg., but had no spontaneous periods. One patient had bleeding only when the progesterone and estrogen were continued, but would fail with either alone.

Secondary amenorrhea for less than 2 years: There were 9 patients with secondary amenorrhea of less than 2 years' duration associated with diminished gonadotrophin and estrogen excretion in the urine.

Seven of these patients received a course of progesterone alone (30 to 60 mg. over 3 days) and bleeding occurred in six. After inducing several menses, three of these patients menstruated spontaneously from three to six months or more, while the other three patients had occasional spontaneous periods after bleedings which were induced with a single injection of 20 mg. of progesterone. The patient who failed to respond at all to progesterone alone had an associated anorexia nervosa. Bleeding could be induced in this patient only with preliminary estrogen priming, which resulted in a marked beneficial psychic effect, resultant gain in weight, and later, spontaneous menstruation.

Another patient in this group had been treated with pituitary and chorionic gonadotrophin (Synapoidin) prior to progesterone, and had responded with three cyclic episodes of bleeding, but later became refractory to this treatment and subsequently responded to progesterone.

Two patients were treated with 300 mg. of anhydro-hydroxy-progesterone alone by mouth and failed to respond with bleeding, but did respond subsequently to 60 mg. of progesterone and later to smaller dosages. Spontaneous bleeding did not occur in either of these cases.

Primary Ovarian Deficiency (Table VI).—

Secondary amenorrhea for more than 2 years: There were 9 patients with secondary amenorrhea of more than 2 years' duration who had developed a primary ovarian deficiency as indicated by high urinary gonadotrophins and diminished estrogens.

TABLE VI. SECONDARY AMENORRHEA

	PRIMARY OVARIAN DEFICIENCY		
	MORE THAN 2 YEARS	LESS THAN 2 YEARS	TOTAL
Number of patients	9	15	24
Bleeding after progesterone alone	1	14	15
Failed with progesterone alone	8	1	9
Subsequent spontaneous bleeding	1	11	12
Had 3 or more spontaneous cycles	0	9	9
Became pregnant	1	3	4
Bleeding after estrogen priming + progesterone	8	1	9
Failed with estrogen priming + progesterone	0	0	0
Subsequent spontaneous bleeding	3	0	3
Had 3 or more spontaneous cycles	0	0	0
Became pregnant	0	0	0

Only one patient of the nine responded with bleeding following progesterone alone in full dosage (60 mg. in 3 days). A. H., aged 25 years, with secondary amenorrhea for two and one-half years' duration, cycled spontaneously after several periods were induced with progesterone alone, and within two months became pregnant and carried to term. During pregnancy she was treated with large dosages of estrogen and progesterone.[9] She had previously miscarried twice.

Another patient had one period with progesterone after the initial period was induced with estrogen, and then failed to respond to further progesterone. S. S., aged 36 years, had amenorrhea of 3 years' duration, hot flashes, and an atrophic vaginal smear. After Premarin daily for 21 days she had estrogen withdrawal bleeding. The following month one flow occurred after the administration of 60 mg. of progesterone. The patient failed to respond to further progesterone therapy without initial estrogen priming.

The additional patients all responded with bleeding when primed with estrogen before repeating the progesterone. Three of these were able to continue with progesterone alone and had occasional single spontaneous cycles; then lapsed into amenorrhea unless progesterone was again given in amounts of 20 mg. or more. Urine hormone assays frequently showed improved estrogen excretion during the course of progesterone therapy. Endometrial biopsies made in two cases late in the cycle following progesterone showed an estrogenic type of endometrium with no secretory changes. The remaining five patients in this group required some estrogen priming before progesterone, although the dosage of the latter could generally be reduced to 20 mg. Best results were obtained when the latter was given as 10 mg. on two successive days. There were four patients in this group who were sterility problems; none became pregnant.

Secondary amenorrhea of less than 2 years' duration: There were a total of 15 patients in this group. Fourteen responded with bleeding to an initial course of progesterone, 30 to 60 mg. over a period of 3 days. After several periods were induced in this fashion with gradually diminishing dosages of progesterone, nine patients had three or more spontaneous menstrual cycles or became pregnant. Pregnancy occurred in three instances, and all three patients went to term, although all received additional estrogen and progesterone during early pregnancy.

The additional six patients required progesterone in amounts of 10 to 30 mg. in order to induce bleeding, and only an occasional spontaneous bleeding occurred.

One patient, B. T., aged 24 years, with secondary amenorrhea for six months and a history of similar episodes earlier, failed to respond to progesterone alone. After priming with ethinyl estradiol and then giving progesterone, three bleedings were induced. No spontaneous cycles followed withdrawal of therapy. This patient had an infantile uterus, and it is probable that in addition to hypogonadism, the endometrium was poorly responsive.

Adrenogenital Syndrome (Table VII).—Four patients with secondary amenorrhea were classified after study as probably having an adrenogenital syndrome. These patients, in addition to amenorrhea, showed marked hirsutism and obesity. Estrogens and gonadotrophins were repeatedly present in the urine in amounts within the normal range. The 17-ketosteroids were in the high normal range in three instances and moderately high (24 mg.) in one case. There was no positive evidence indicating an adrenal cortical tumor or a Cushing's syndrome in any of these cases.

TABLE VII. SECONDARY AMENORRHEA

ADRENOGENITAL SYNDROME

	MORE THAN 2 YEARS	LESS THAN 2 YEARS
Number of patients	2	2
Bleeding after progesterone	2	2
Failed with progesterone alone	0	0
Subsequent spontaneous bleeding	1	0
Had 3 or more spontaneous cycles	1	0
Became pregnant	0	neither
	1 married	married

Bleeding was induced in all four patients following the injection of progesterone in a dosage of 30 to 60 mg. over three days.

In one instance, F. N., aged 28 years, three spontaneous bleedings occurred. The endometrium in this case which prior to treatment was of the early interval type, showed late secretory changes in the cycle following progesterone therapy. This patient, who was a sterility problem, did not become pregnant.

Progesterone in dosage of 10 to 30 mg. was required to induce further bleeding in the three remaining cases.

Summary of Results of Treatment in Various Groups

In Table VIII there is summarized results of treatment with high dosage progesterone with and without estrogen priming, the relationship of the type of amenorrhea, the hormonal status of the patient, and the duration of the amenorrhea. It will be noted that bleeding was eventually induced in 49 of the 51 patients. In 29 cases, or 57 per cent, bleeding occurred following high dosage progesterone alone, while in 20, or 95 per cent, of the remaining 21 cases treated, bleeding occurred when estrogen was added to progesterone therapy. Subsequent spontaneous bleeding occurred in a total of 29, or 57 per cent, of the cases but only 19, or 37 per cent, had three or more spontaneous cycles. A total of 8, or 27 per cent, of the 30 married women in this group became pregnant, and all carried to term except one.

TABLE VIII. SUMMARY OF RESULTS

	TYPE OF AMENORRHEA		HORMONAL STATUS*		DURATION		
	PRIMARY AMENORRHEA	SECONDARY AMENORRHEA	GONADOTROPIC DEFICIENCY	PRIMARY OVARIAN DEFICIENCY	MORE THAN 2 YEARS	LESS THAN 2 YEARS	TOTAL GROUP
Number of patients	7	44	18	28	25	26	51
Bleeding after progesterone	0	29	10	15	5	24	29
Subsequent spontaneous bleeding		21	8	12	4	17	21
Had 3 or more spontaneous cycles		15	5	9	2	12	15
Became pregnant		5	1	4	2	4	6
Bleeding after estrogen priming + progesterone	5 of 6 treated	15	8	13	18	2	20
Failed with estrogen priming + progesterone	1	0	0	0	1	0	1
Subsequent spontaneous bleeding	1	6	3	4	7	1	8
Had 3 or more spontaneous cycles	0	3	3	0	3	1	4
Became pregnant	0	1	1	0	2	0	2

*In addition there were 4 patients with adrenogenital syndrome and one with primary uterine defect.

High Dosage Progesterone as a Clinical Test for Pregnancy in Patients With Recent Amenorrhea

We treated 18 young women with delayed menstruation of only two weeks to three months' duration. In all of these cases, a question of pregnancy arose which was checked by the Friedman test. At the same time, these patients were started on 20 mg. of progesterone on each of two or three successive days. The results are given in Table IX. In 17 of the 18 cases, pregnancy or its absence was properly indicated by the clinical results; i.e., whether or not bleeding was induced within three to five days after the last injection. In one patient who received 40 mg. of progesterone after two weeks of amenorrhea, no bleeding occurred for five weeks. It is probable that this patient at the time of injection

TABLE IX. HIGH DOSAGE PROGESTERONE AS A CLINICAL TEST FOR PREGNANCY

	PATIENTS	WITHDRAWAL BLEEDING	FRIEDMAN TEST NEGATIVE	NO BLEEDING	FRIEDMAN TEST POSITIVE
Progesterone 40 mg. (20 mg. on 2 days)	8	5	5	3*	2
Progesterone 60 mg. (20 mg. on 3 days)	10	6	6	4	4
Total	18	11	11	7	6

*In one of these bleeding finally occurred after three weeks.

was in the corpus luteum phase of a delayed cycle, since Zondek,[1] has shown that progesterone will not produce bleeding during this phase. Zondek has also indicated, and it has frequently been corroborated by us, that progesterone and estrogen in the dosage used in the treatment of amenorrhea will have no harmful effects upon a normal pregnancy.

As a clinical procedure in patients with suspected pregnancy, high dosage progesterone therapy is of value because it will usually induce bleeding promptly in patients who are desirous of having a menstrual flow if they are not pregnant.

Discussion

High dosage progesterone therapy has proved to be a valuable adjunct in the treatment of functional amenorrhea. When used alone in patients with recent amenorrhea, it will usually induce bleeding, while when used in conjunction with estrogens, bleeding can regularly be induced except in those rare instances where there is an associated uterine defect or if the woman is pregnant. Even the patient with primary amenorrhea can be made to bleed, although invariably this requires priming with estrogen and full dosage of progesterone or the simultaneous injection of both. However, the patients with primary amenorrhea will rarely have a spontaneous bleeding even after repeated induced flows, while a proportion of these will have one or more spontaneous flows, particularly if their amenorrhea is of recent origin. These observations confirm those originally made by Zondek.

Our studies further indicate that these results may be expected in patients with various types of sex-endocrine dysfunction. In patients with primary amenorrhea, whether due to a gonadotrophic deficiency or, as is more common, due to a primary ovarian deficiency, estrogen is required to obtain bleeding with full dosages of progesterone. Zondek early pointed out that at least minimal amounts of estrogen must be present to obtain a reaction with progesterone, but that even this minimal amount is apparently not present in women with true primary amenorrhea. In the cases of secondary amenorrhea, a high percentage of good results can be expected with progesterone alone whether the patient has a primary gonadotropic or primary ovarian deficiency, provided the amenorrhea is of less than two years' duration, whereas, in both groups, if the amenorrhea is of longer duration, additional estrogen is required. This is of especial interest in that estrogen deficiencies, as determined by urinary hormone assays, vaginal smears, and endometrial biopsy were equally marked in most members of both groups. This raises the question as to whether the uterus becomes increasingly refractory as the amenorrhea persists. Further investigations on castrate women are under way to determine this point. On the other hand, in the patients in whom the amenorrhea was asso-

ciated with good urinary estrogen values (believed to have an adrenogenital syndrome) bleeding occurred with progesterone alone despite the duration of amenorrhea, which in one case was of 10 years' persistence. This latter group constitutes an exception to the generalization that amenorrhea of more than two years' duration requires administration of estrogen in addition to progesterone to induce bleeding.

The study of the urinary hormone assays following progesterone, or estrogen plus progesterone, indicates that an improvement in the hormonal pattern is noted in many instances of secondary amenorrhea, whether caused by a gonadotropic or primary ovarian deficiency. In the former group, there is frequently an increase in the gonadotrophin and estrogen titer, particularly in the month or two following injection, and is no doubt responsible for the spontaneous cycling in some of these patients, and for the improvement in the endometrial biopsy as well as the occasional pregnancy. This at first suggests that progesterone may have a favorable "back-action" on the pituitary. Such an hypothesis is hardly supported by our knowledge of progesterone physiology. In many species, estrogen is believed to suppress the follicle stimulating function of the pituitary and under certain conditions to promote the release of luteinizing hormone,[10] while progesterone suppresses the release of luteinizing hormone;[11] whether this in turn may be followed by a release of the follicle-stimulating hormone in women under the conditions in which it is here employed is not known, but certainly requires further study.

In women with a primary ovarian hypofunction, the majority of our hormonal findings seem to indicate an entirely different mechanism. Here the primary change seems to be an improved estrogen excretion following high dosage progesterone therapy, even in those instances in which estrogen was not given in the previous cycle; frequently, but not always, there was a reduction of high gonadotrophin levels to more nearly normal values. These findings suggest that the ovary has become more responsive to gonadotropic stimulation. In this regard, it is of interest that the patients in this group who had amenorrhea of more than two years' duration or who had frank menopausal symptoms were less likely to show this type of improvement or to menstruate spontaneously. It is of interest, however, that one young woman in this group did have two spontaneous cycles, became pregnant, and carried to term. Such observations suggest that there is a profound difference between the ovary of the young woman with a temporary primary ovarian deficiency and a patient with a frank menopausal syndrome, despite the similarity in their hormonal patterns.

Our observations in patients believed to have an adrenogenital syndrome are not sufficient to draw any conclusions concerning the mechanism of bleeding. Probably the large amount of progesterone administered reduces the total estrogenic effect with resultant withdrawal bleeding. Such a theory would explain why three of our patients in this group failed to cycle spontaneously at any time; however, one patient in this group not only cycled spontaneously three times, but, on one occasion at least, developed a typical secretory endometrium.

Our clinical and laboratory studies have led us to believe that high dosage progesterone therapy has a distinct place in the treatment of certain types of impaired fertility in the female, especially when associated with hypomenorrhea or secondary amenorrhea. When the condition is associated with gonadotropic deficiency, stimulation therapy with gonadotropic hormone is generally the treatment of choice. The difficulties attendant upon the prolonged continuation of such treatment, particularly because of the possibility of producing cystic ovaries[12] or antigonadotrophins[13] often make it expedient to change to progesterone after three months on gonadotropic hormone. In primary ovarian deficiencies in young women, high dosage progesterone would appear to be the treatment of choice since it obviates the use of prolonged estrogen therapy which, during the time of administration, would certainly tend to inhibit ovulation. Finally, in the young sterile women with amenorrhea or hypomenorrhea, the induction of regular bleeding episodes avoids much psychological trauma when the patient is anxious to believe that she may be pregnant. If pregnancy does occur, this type of therapy does not prove harmful as shown by Zondek[1] and by our observations; indeed, the failure to bleed arouses suspicion that pregnancy has occurred.

Summary

1. A total of 51 amenorrheic patients were treated with high dosage progesterone with or without additional estrogen. Seven of the patients had primary amenorrhea, while in 44 of the cases, secondary amenorrhea was present. In 25 of the cases the amenorrhea was of more than two years' duration. From the endocrine standpoint, 18 of the patients had gonadotropic deficiencies, 28 of the patients had a primary ovarian deficiency. Four patients were believed to have an adrenogenital syndrome, and one patient had a primary uterine defect.

2. In the 25 patients with amenorrhea of more than two years' duration, only 5, or 25 per cent, responded with bleeding to progesterone alone, whereas 24, or 92 per cent, of the 26 patients with amenorrhea of lesser duration bled.

3. None of the patients with primary amenorrhea had bleeding after 60 mg. of progesterone, while 5 of the 6 who were given progesterone after estrogen priming had induced bleeding. Only one spontaneous bleeding occurred after withdrawal therapy. The patient who failed to respond at all had an endometrial defect.

4. Of the 44 patients with secondary amenorrhea, 29, or 66 per cent, responded to progesterone alone. Many of these had subsequent spontaneous bleedings, and five became pregnant. The remaining 15 patients had induced bleeding with progesterone after estrogen priming. A smaller percentage of these patients had subsequent cycles and only one became pregnant.

5. The patients with a gonadotropic deficiency and a primary ovarian deficiency responded approximately equally well so far as induction of bleeding was concerned. In both of these groups there was a tendency for the hormonal status to improve immediately following treatment as indicated by

increased gonadotropic production in the first group and better ovarian response (increased estrogens and improved endometrium) in the second group.

6. Four patients with secondary amenorrhea due to adrenogenital syndrome responded with bleeding to progesterone therapy alone, even if the amenorrhea was of long duration. The endocrine status of these patients did not improve.

7. Eight (27 per cent) of the 30 married women became pregnant following therapy.

8. An additional group of 18 patients with delayed menstruation or recent amenorrhea who were suspected of pregnancy were treated with 40 to 60 mg. of progesterone, 20 mg. on two or three successive days. As checked by the Friedman test, bleeding failed to occur if pregnancy was present, whereas in all but one instance bleeding was induced in the nonpregnant patients.

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Discussion

DR. ARTHUR FIRST.—From a practical standpoint, Dr. Rakoff's interesting paper brings up the important question—does progesterone afford us a worth-while addition to our therapeutic armamentarium in the treatment of amenorrhea? I think Dr. Rakoff's studies show that in many instances it does, especially in an estrogen primed endometrium.

Even the advisability of treating amenorrhea is a controversial subject today. Take for example Greenhill's statement in the 1944 *Year Book of Obstetrics and Gynecology* to the effect, "I am opposed to treating amenorrhea except in young girls who have not begun to menstruate by the time they reach 18 and in married women who desire children. I see no reason at all to treat women who have scanty menstruation or infrequent menses. I think they are fortunate in losing only a small amount of blood."

In spite of this, I agree with Dr. Rakoff when he cites the "psychological trauma" of these amenorrheic individuals. I also believe that, untreated, the endocrine deficiency may ultimately result in permanent damage to the ovaries and uterus.

It must be admitted, however, that our present-day treatment of amenorrhea is far from satisfactory. For permanent cure, my own first love is still low dosage irradiation of the pituitary gland and ovaries, but I will be only too happy to abandon it for the more rational hormone therapy if it be shown to be equally as effective.

The use of progesterone brings up some interesting questions, "Is it substitutive or stimulative?" Dr. Rakoff's studies seem to indicate that, although usually only the former, it can be both, as pregnancy has actually ensued in some cases, in 1 case after low dosage irradiation had failed.

I would like to ask Dr. Rakoff whether he is convinced that progesterone withdrawal bleeding cannot be induced during pregnancy, especially if very large doses are administered?

Several years ago I read a paper before this society on the inadequacy of the treatment of threatened abortion with progesterone. I cited several patients who, threatening to abort, seemed, after a week of rest, sedation, vitamin E, etc., to have quieted down, when a single injection of 10 mg. of progesterone was followed within 24 hours by a miscarriage.

Hamblen made similar observations. Pregnandiol titers were actually decreased by injections of progesterone. The concomitant administration of estrogens and progesterone at times resulted in some increase in pregnandiol. The only definite increases in pregnandiol titers followed the simultaneous administration of chorionic gonadotrophins and estrogen in addition to the progesterone.

In his paper, Dr. Rakoff states that "progesterone in some instances suppresses the release of luteinizing hormone." Could this not in certain cases actuallly defeat the purpose by inhibiting the patient's own progestin so essential for nidation to continue? In other words, is progesterone completely harmless as a pregnancy test? Dr. Rakoff states that "the failure to bleed arouses suspicion that pregnancy has occurred." Might it not also precipitate bleeding if given in very large doses? My own thought would be to rule out pregnancy first by other means before resorting to large doses of progesterone.

DR. MAHLON HINEBAUGH.—First, we have the observation that, especially in obese women, reduction of fat is followed by the establishment of a somewhat regular menstrual cycle. With these instances of investigation, have you done routine basal metabolic rate studies in order to determine thyroid function in women receiving this progesterone and combined therapy?

DR. RAKOFF (Closing).—Concerning the remarks by Dr. First, I am in agreement that we must be extremely cautious concerning the use of progesterone in the induction of bleeding in patients who might be pregnant. I would hardly advocate the use of progesterone as a routine clinical test for pregnancy at the present time. Thus far in our cases we have never seen high dosage progesterone induce bleeding in pregnancy, and Zondek had the same experience. I do not feel progesterone alone is the best type of medication for a patient who is pregnant and showing evidence of threatened miscarriage. It is very important to add estrogen to this progesterone; it is of course possible that progesterone may inhibit the patient's own endogenous progesterone production. High dosage progesterone has never induced bleeding in the patients who were pregnant. Concerning the mechanism, I think it is puzzling. Our observations answer nothing, but raise many more questions.

Dr. Hinebaugh raised the question of weight reduction and thyroid function with regard to amenorrhea, and I agree that weight reduction is an important part. I would like to add that progesterone is not the answer to all types of amenorrhea treatment. It is simply one approach that can be used. The patients we presented were all thoroughly investigated, and there were none in this group with thyroid deficiencies. None were unusually obese except the group of adrenogenital syndrome; that group was put directly on progesterone therapy and not tried first on weight reduction.

A REVIEW OF THE MATERNAL MORTALITY AT THE CHICAGO LYING-IN HOSPITAL, 1931-1945

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GREAT strides have been made during the past fifteen years in the reduction of maternal deaths in childbirth. The curve is still continuing downward, for the irreducible minimum has not been reached. The great improvement in our special field is the result of many factors. The education of the profession, the education of the lay public, better hospital facilities, and, most important, the dramatic advances that have taken place in the practice of medicine.

Obstetrics has been the beneficiary of all the knowledge in medicine and the basic sciences. The use of blood and plasma, the sulfonamides and penicillin, safer and more efficient methods of pain relief and anesthesia, have all contributed greatly to the dramatic reduction of maternal mortality. However, the extension of our knowledge to the profession and to the public has helped materially to bring these benefits to the patient.

The Chicago Lying-in Hospital admits all women who apply for care without regard as to their ability to pay if their condition warrants specialized care. About 75 per cent of the patients are under the care of a full-time attending staff who are members of the Department of Obstetrics and Gynecology of the University of Chicago. All of these patients are used for teaching, directly or indirectly. The remaining 25 per cent of patients are delivered by a visiting staff, most of the members of which have have had special training. The conduct of these patients is subject to review by the attending staff. Consultation during pregnancy and labor is made extremely easy for the patient and her physician, in order to encourage the full use of all the facilities of the institution.

Most of the maternal mortality studies concern themselves with communities at the local, state, or national level. They represent a cross section of obstetric practice in which the general practitioner, the specialist, the small and the large hospitals, all play a role. The teaching institutions have published their statistics, but these have rarely been subjected to the close scrutiny and the cold impartial analysis that all maternal deaths deserve. Generally, it has been recognized that the teaching services, with their carefully trained staffs and their exceptional facilities, have had better results than the rest of the community. However, it has not been sufficiently emphasized that teaching services train young people in the specialty and that there is an increased hazard in the training of a staff. Obstetrics is often emergency medicine, and, in spite of close

*Presented before a meeting of the Chicago Gynecological Society, Feb. 16, 1945.

supervision of the junior staffs, many complications do arise which must be charged to inexperience. The teaching of young physicians is done at a cost which can be kept down to a minimum, but it must be reckoned with.

This report is a careful appraisal of the maternal deaths at the new Chicago Lying-in Hospital, covering a period of thirteen and one-half years. Each death was subjected to a detailed study by the authors, following which all the factors involved were analyzed by the senior members of the staff. The death was considered preventable or not preventable. Preventable factors were always charged to the physician, the institution, or the patient. Although the primary cause of death was determined in each instance, many contributory factors often made the primary cause inevitable. The patient who sustained a rupture of the uterus probably died of hemorrhage within a short time of the trauma, and the death would be accounted for under this primary heading, or she may have survived for some days or even weeks to succumb ultimately of infection. The primary cause of death does not tell the complete story in every case for the contributory factors may make the ultimate outcome inevitable.

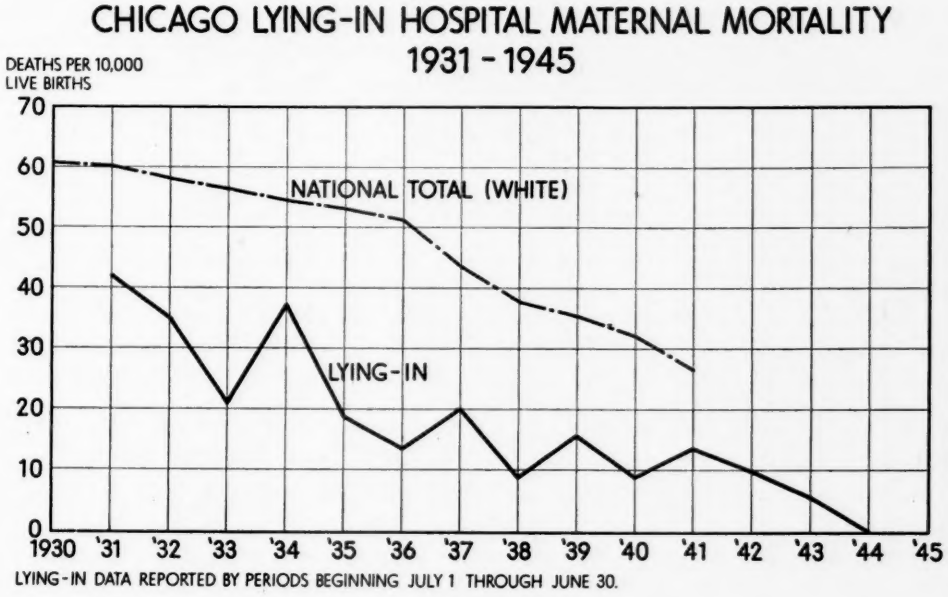

Fig. 1.

Maternal mortality at the Chicago Lying-in Hospital has decreased steadily during the last thirteen and one-half years and the curve parallels the national curve (Fig. 1). The most rapid decline has occurred in the last four years. The improvement of maternal mortality in the last two years may be due partly to the discontinuation of deliveries in the home.

There were 81 deaths in 47,945 obstetric patients, an over-all mortality of 0.17 per cent of all pregnant patients. It is well to point out that Fig. 1 lists the deaths per 10,000 live births so that the figures can be compared with Bureau of Census data.

TABLE I

Deliveries in the hospital	39,719
Deliveries in the home	6,701
Abortions managed in the hospital	1,738
Ectopic pregnancies	132
Total number of pregnant patients	47,945
Total deaths	81 or 0.17%

TABLE II

Delivered and died in the hospital		64
Delivered in the home and died in the hospital		11
Delivered by home service or C.M.C.	9	
Delivered by private physicians	2	
Delivered and died on home service		3
Delivered in hospital but died at home		2
Sent from home service to Cook County		1
Total number		81
Maternal mortality		0.17%

TABLE III

AGE (YEARS)		
Average age		29.4
Oldest patient		43.0
Youngest patient		19.0
DURATION OF PREGNANCY		
More than 36 weeks		53
From 30 to 36 weeks		11
From 20 to 29 weeks		9
Under 20 weeks		8
Criminal abortion	3	
Ectopic gestation	2	

Table I shows the distribution of cases in the hospital and in the home as well as abortions and ectopic gestations. All the deaths are included in this report.

In Table II it will be noted that 64 of these patients were delivered and died in the hospital; 11 were delivered in their homes by the Home Service, the Chicago Maternity Center, or a private physician and were sent to the hospital in the postpartum period; 3 women were delivered and died in their homes; 2 women were delivered in the hospital but died at home within the first eight weeks after delivery; one patient was sent to another hospital by the Home Service and died there.

The age of the patients who died may be of some interest. The youngest patient was 19 and the oldest 43 years. The average age of the group was 29.4 years (Table III). Eastman has pointed out recently that youth is a better safeguard against the complications of pregnancy and labor than child spacing. His report once more emphasizes the increased hazards of childbirth late in the reproductive career.

In 53 patients the duration of pregnancy was longer than thirty-six weeks; in 11 from thirty to thirty-six weeks; in 9 from twenty to twenty-nine weeks; and 8 women were less than twenty weeks pregnant when they died (Table III).

Thus, 17 women, or 21 per cent, were less than twenty-nine weeks pregnant. In 3 patients death followed a criminal abortion. Ectopic pregnancy resulted in a fatal outcome in two patients.

The causes of death in the 81 women is portrayed in Fig. 2. In general, our mortality figures follow the general pattern. Infection is the principal cause of death, accounting for 39.5 per cent of the total. This compares with the national figure of 38 per cent for the year 1941. Hemorrhage and shock, however, contribute 16 per cent, whereas the toxemias of pregnancy contribute 7.4 per cent. These compare with 26 and 25 per cent for the country at large (Fig. 3). Heart disease ranks high in our statistics, for it accounts for 16 per cent of the deaths. Autopsies were performed in 77 per cent of the 81 patients who died.

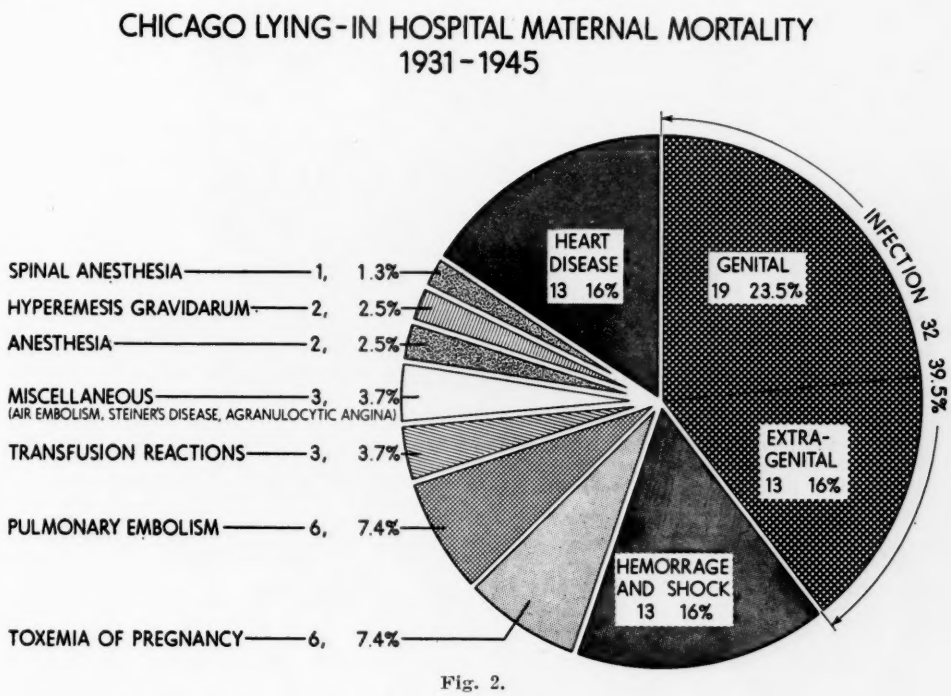

Fig. 2.

A careful analysis of the clinical histories indicates that preventable factors were present in two-thirds of the patients who died (Table IV). In only one patient out of three was the death considered not preventable. Many factors enter into the medical care of an obstetric patient, some of which play vital roles in the ultimate outcome. The patient with serious heart disease who refuses early therapeutic interruption because of her convictions must share in the responsibility of the conduct of so serious a hazard. Unintelligent prenatal care by the physician lulls many a patient into a sense of security that the exigencies

TABLE IV

Total number of deaths	81
Preventable factors present	54—66%
Not preventable	27—33%

of the case do not merit. The lack of proper facilities for the care of the patient or the complicated armamentarium necessary to safeguard delivery must be charged to the institution. Inexperience on the part of the attendant and the failure to recognize omens of danger or the inability to cope with complicated procedures must be laid at the door of the physician. There is an inevitable mortality in obstetrics, but much progress must be made before the irreducible minimum has been reached.

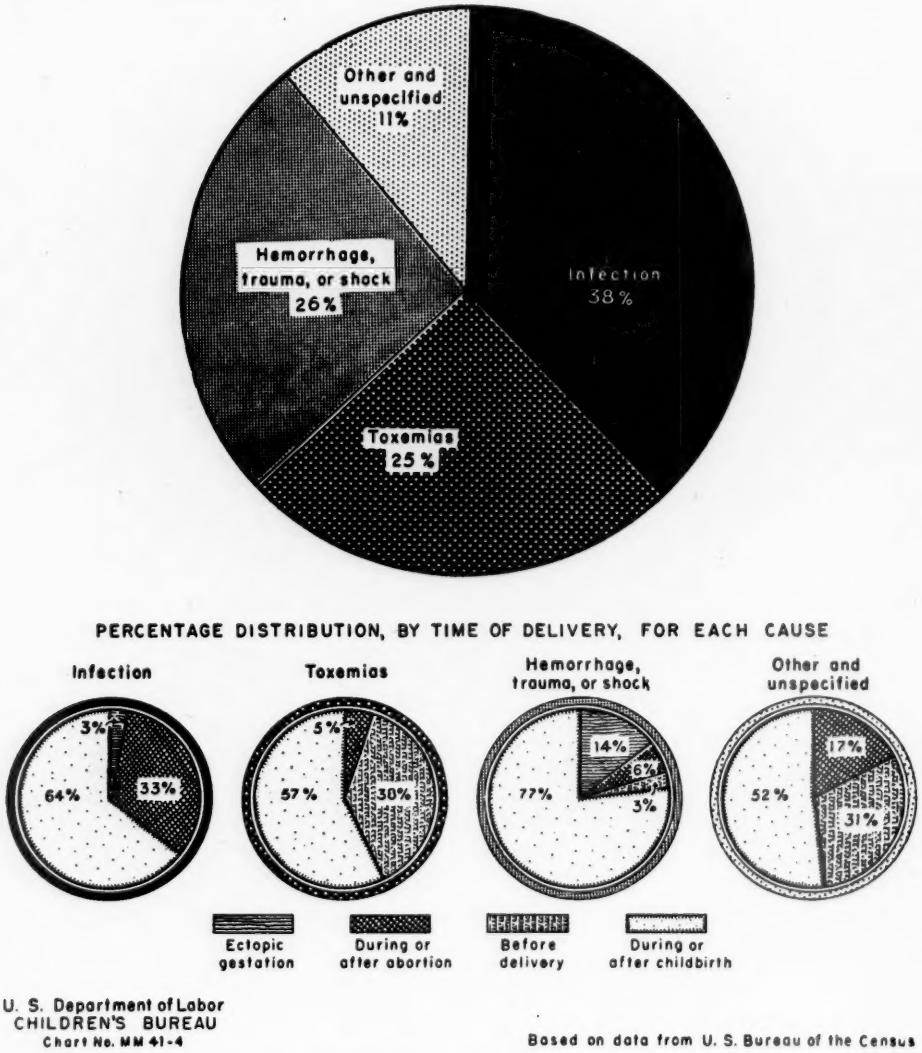

Fig. 3.—Causes of maternal death in the United States, 1941 (percentage distribution, by cause.)

Infection

A tremendous change is evident in the principal causes of maternal mortality during the last five years. If our statistics are an example of the trend in the large institutions, infection is rapidly disappearing as a major cause of death in obstetrics. This change in maternal mortality, however, is not mani-

TABLE V. INFECTION AS CAUSE OF DEATH

INFECTION			
Genital in origin			19
Extragenital in origin			13
Tuberculosis		4	
Pneumonia		5	
Meningitis (other than Tb.)		2	
Diphtheria		1	
Ruptured appendix		1	
Before July 1, 1939		*July 1, 1939, to Jan. 1, 1945*	
Deliveries			
Hospital	21,840	17,879	
Home	4,606	2,090	
Total	26,446	19,969	
Genital infections	19	0	
ORGANISMS IN GENITAL INFECTIONS			
Hemolytic streptococcus			9
Anaerobic streptococcus			4
Bacillus welchii			2
Other			4

fest as yet in the statistics of the country at large nor in those of the large urban centers. The well-equipped, well-staffed, competently managed maternity has finally become the safest place in which women can have babies.

The disappearance of infection as a major cause of death can be ascribed to a number of factors. First and foremost is the introduction of the sulfonamides and penicillin. Their intelligent therapeutic application has removed the fangs of that ever present specter, infection. These drugs and antibiotics are not applicable to all the virulent organisms involved in puerperal infection, but increasing knowledge will undoubtedly result in new substances effective in an ever-increasing variety of organisms. Preliminary reports concerning the most recent antibiotic, streptomycin, are enthusiastic. More intelligent management of peritonitis has decreased the hazard of this complication. The institution of duodenal drainage by Wangensteen method of constant siphonage and the Miller-Abbott tube has decreased distention and vomiting in peritonitis. Decompression of the distended abdomen decreases the spread of infection, and rest to the intestinal tract promotes localization.

The liberal use of blood, plasma, and parenteral fluids have provided efficient tools for the treatment of infection. The anemic patient is more vulnerable to infection and, once developed, the course is likely to be more virulent than in the patient who has a normal blood picture. Infection is hard on the blood constituents, particularly when the organism is hemolytic in character. Constant blood replacement may be necessary to maintain the body defenses at their optimum efficiency. Lastly, better obstetrics has decreased the hazards of infection. The careful evaluation of cephalopelvic disproportion has decreased the incidence of prolonged labor with its dire consequences. The elimination of the high forceps and the difficult midforceps deliveries has decreased the extent of trauma and resultant infection. The carefully conducted test of labor has increased the safety of cesarean section. Difficult obstetrics has been

made more simple as a result of intelligent approach to the problems of labor and delivery.

Infection is the most frequent cause of death in the present series of cases, accounting for 32 deaths, or 39.5 per cent of all deaths (Table V). The inflammatory process was genital in origin in 19 instances and extragenital in 13. Four of the extragenital deaths were due to tuberculosis and 5 to pneumonia. The streptococcus was the organism involved in 13 of the 19 cases of puerperal infection, and in 4 it was anaerobic in character.

The most interesting observation is that all the deaths from puerperal infection of genital origin occurred prior to July 1, 1939 (Table V). During this period, there were 26,446 deliveries in the hospital and on the home service. Since that date almost 20,000 women were delivered without a single death due to puerperal infection. Thus, it is not too much to hope that the major cause of maternal mortality will ultimately disappear, or its importance become greatly reduced.

Hemorrhage

Deaths from hemorrhage and shock comprise the second most common cause of death in our clinic. In 13 cases it was the primary cause, although it was a contributory cause in many other fatalities (Table VI). Three women who died because they received incompatible blood would have been alive if a transfusion was not indicated. Furthermore, at least 25 of the women who died lost more than 500 c.c. of blood. In 15 instances the blood loss was more than 1,000 c.c., whereas one patient with a ruptured uterus lost 3,300 c.c. Five of the women who lost more than 500 c.c. of blood ultimately died of infection and are charged to this cause. Thus, an excessive loss of blood influenced directly or indirectly the clinical course of almost one-half of these women who lost their lives in childbirth.

Hemorrhage and its resultant shock is a preventable complication in many cases; it is amenable to adequate therapy in most cases. There are many obstetric complications in which hemorrhage plays the dominant role and the man-

TABLE VI. HEMORRHAGE

PATIENT	ETIOLOGY	PREVENTABILITY	AUTOPSY
C.	Abruptio placentae	Yes	Yes
D.	Placenta previa	Yes	Yes
D.	Postpartum hemorrhage	Yes	Yes
S.	Postpartum hemorrhage (Submucous fibroid)	Yes	No
P.	Postpartum hemorrhage (Pre-eclampsia)	Yes	No
S.	Postpartum hemorrhage (Retained placental fragment)	Yes	Yes
S.	Intra-abdominal hemorrhage (Omental)	Yes	Yes
N.	Ruptured ectopic	Yes	Yes
B.	Ruptured uterus	Yes	No
M.	Ruptured uterus	Yes	Yes
L.	Ruptured uterus	Yes	Yes
P.	Ruptured uterus	Yes	No
M.	Ruptured uterus	Yes	Yes

agement includes the proper treatment of the etiological causes. Early in pregnancy, abortion and ectopic gestation are the principal causes of pathologic blood loss. Late in pregnancy, placenta previa and abruptio placentae account for most of the serious hemorrhages. During delivery, trauma and postpartum bleeding associated with the placental stage contribute chiefly to death from excessive bleeding.

In the management of any of these complications, blood loss must never be lost sight of. Ideally, the amount lost must be kept within safe limits, but, when that is not possible, preparations must be made to replace the blood lost. One of the brightest chapters in World War II has been the rapid extension in the use of blood and its constituent fractions. The ease and the simplicity of their administration under the most unfavorable of circumstances must serve as an object lesson for all maternities. Blood and plasma must be readily available at all times and in liberal amounts.

Two of the deaths in this series are charged to placenta previa. During the period covered by the report this diagnosis was made in 271 cases, an incidence of 0.6 per cent of all deliveries. The mortality of placenta previa in our hospital was 0.72 per cent. The two patients who died were treated by cesarean section and, in both instances, their deaths are considered preventable by present standards. The first patient died because of hemorrhage. The extent of the blood loss was not recognized by the attendant who did not have sufficient clinical experience. Preparations for the restoration of the lost blood were delayed and as a result she received too little blood too late to save her life. The second patient entered the hospital because of painless bleeding at about thirty weeks' gestation. A vaginal examination was done and a diagnosis of incomplete placenta previa established. Contrary to the usual practice the delivery was delayed for a week, when a sudden recurrence of bleeding necessitated immediate intervention. A cesarean section was done. Her postpartum course was febrile as a result of pelvic thrombophlebitis. Following several pulmonary infarcts she died on the sixteenth day of massive pulmonary embolism.

The management of placenta previa has become fairly standardized in our institution; although one of the major causes of maternal mortality, proper treatment can reduce this hazard to a minimum. Early recognition of the presence of abnormal placental location is essential. Patients are requested to come into the hospital at the first indication of bleeding. They are typed and matched and blood is made available. The diagnosis of placenta previa is established on pelvic examination. In the event no placental tissue is palpable in the region of the cervical os, the patient is sent home. If the placenta can be palpated covering part or all of the os, a decision is reached as to how best to terminate the pregnancy. Other factors than the degree of previa will influence the choice of treatment.

If the os is partially covered by placenta (incomplete placenta previa) delivery from below is favored. Simple rupture of the membranes may suffice to control the bleeding and to initiate labor. Where this procedure is effective, its simplicity assures the greatest safety from the two hazards of placenta previa, bleeding, and infection. In the event that rupture of the membranes fails to

control bleeding, Willet's method of scalp traction adds no great hazard to the management of placenta previa. Scalp traction properly applied need do no serious damage to the baby. In the patient with a previable fetus, this procedure may prove ideal. The use of Braxton-Hicks' version, as well as the insertion of a bag, have no real place in the modern management of placenta previa. Extensive manipulation through the pathologic lower uterine segment is fraught with too great danger of trauma and its sequelae, hemorrhage and infection. It is interesting to note that 160, or 59 per cent, of all the placenta previa cases at the Chicago Lying-in Hospital during the last thirteen and one-half years were delivered vaginally, and all of the women survived. This result can be charged to the careful selection of patients for this mode of delivery as well as to the meticulous care exercised in their therapy.

Patients with complete placenta previa, the whole os covered over by placental tissue at the time of examination, are best treated by cesarean section. The hazards of delivery through the natural passages far outweigh those of cesarean section. The operation should be carried out when the diagnosis is established. Delay may increase the likelihood of infection. Had this rule been followed, one of the two women with placenta previa who died may have survived. Other factors than the location of the placenta may favor cesarean section as the choice of treatment. Patients who have suffered marked blood loss, the presence of a borderline pelvic contraction, or elderly primiparity may influence the decision for an abdominal delivery in the presence of incomplete placenta previa. In the presence of gross genital infection, abdominal delivery should include hysterectomy, or peritoneal contamination can be avoided by an extraperitoneal operation.

Abruptio placentae was present in 237 patients, an incidence of 0.5 per cent of all our deliveries. Two patients died, a maternal mortality of 0.84 per cent. In both instances the delivery was accomplished vaginally. One of these two deaths was considered preventable.

The mild cases of abruptio placentae can be treated by conservative methods. Rupture of the membranes to hasten the labor, and instrumental delivery of the fetus with an impaired circulation may suffice to save the baby and its mother.

Serious abruptio placentae is a major complication which entails considerable risk for the mother. Most often associated with vascular-renal disease, it probably represents a local obstetric manifestation of this disorder. The patient who goes into active labor after the accident and makes rapid progress because of the tumultuous contractions should be delivered vaginally. However, that this so-called conservatism does not always end uneventfully can be seen in the fact that the two deaths in our series occurred in patients who were delivered from below. The patient who presents a picture of massive hemorrhage, behind the placenta, into the wall of the uterus and retroperitoneally, is better treated by cesarean section. If the uterus fails to contract after emptying its cavity of the dead fetus and the clots, hysterectomy should follow. We have never regretted the decision to remove the uterus because of hemorrhagic extravasation,

but in two instances it was necessary to remove it secondarily, two and six hours after the initial operation. In 71 patients with abruptio placentae, cesarean section was the method of treatment.

The liberal use of blood during labor, delivery, and the puerperium is the most important measure to safeguard the life of the patient. Plasma and parenteral fluids are useful adjuvants, but in the patient who has lost large amounts of blood from the circulation, only whole blood will safeguard her life.

Postpartum hemorrhage as a result of other causes than placenta previa and abruptio placentae accounted for at least four of the thirteen deaths. Excessive blood loss during the third stage of labor was an important factor in at least one-third of the entire series of patients. All four deaths are considered preventable in the light of our present knowledge.

The incidence of postpartum hemorrhage is usually given as 5 or 6 per cent, but modern management of the third stage has resulted in a marked reduction. During the years 1940 to 1943, almost 10,000 women were delivered at the hospital and a diagnosis of postpartum hemorrhage was made in 114, an incidence of 1.1 per cent. Uterine atony in the absence of any other demonstrable cause was present in 36 per cent; trauma in 25.5 per cent; placental fragments in 15.7 per cent; placenta previa and abruptio placentae in 21 per cent; fibroid tumors in 1.8 per cent. These are the usual causes of excessive blood loss and they must be kept in mind in order to approach the therapy logically.

The most common cause of excessive blood loss in the third stage is the mismanagement of this important period. Premature attempts at placental expression before its complete separation results in uterine atony and bleeding. If a natural physiologic third stage is to be awaited, there must be no interference until the placenta has been completely separated following which it can be expressed. However, in hospital practice the placental stage can best be managed artificially by the use of an oxytocic drug. The routine conduct at the Chicago Lying-in Hospital is to administer intravenously 0.2 mg. of ergonovine as the head is being delivered. About thirty to sixty seconds are allowed to elapse before the body is delivered, to give the drug a chance to exhibit its action. Placental separation occurs during the initial contraction of the uterus which follows its emptying. The sudden reduction in the surface area of the placental site results in a rapid clean, and complete separation. The placenta is then expressed promptly. This routine has resulted in a two-thirds reduction in the frequency of postpartum hemorrhage.

Placental fragments remaining attached to the uterus will provoke uterine atony and bleeding. The placenta must be examined most carefully to determine if it is complete and for the possibility of an accessory cotyledon remaining attached to the uterus. If there is any doubt about the placenta, immediate uterine exploration is a safe procedure when carried out under stringent asepsis. Retained placental fragments were responsible for at least two deaths in this series. One of these patients died of hemorrhage shortly after delivery; the other survived long enough to die of puerperal thrombophlebitis and sepsis.

Trauma is a major cause of postpartum bleeding. Careful exploration of the reproductive tract should be instituted whenever the placenta is out of the

uterus and ergonovine intravenously fails to control the bleeding. If the lower genital tract does not reveal the source of the bleeding, the lower uterine segment and corpus must be examined. Rupture of the uterus was present in 7 of the 81 patients in this group. Suture is the only safe way to control traumatic bleeding.

One of the patients who died of hemorrhage immediately after delivery had a submucous fibroid in the wall of the uterus. The usual therapy failed to control the bleeding and hysterectomy was delayed too long to save her life.

Postpartum hemorrhage must be managed in a logical manner rather than by haphazard means. Excessive bleeding prior to placental expulsion cannot be controlled until the placenta is out of the uterus. Credé's expression should be tried, but if it fails, manual removal without too great delay is indicated. A good oxytocic drug administered intravenously (ergonovine or pituitary extract) should now control the bleeding. Further hemorrhage calls for a careful exploration and inspection of the reproductive tract for retained fragments of placenta, trauma, or neoplasms. In the absence of these, an oxytocic drug may now be administered a second time on the assumption that the first did not get into the vein. Uterine tamponade may be indicated, rarely. Hysterectomy is a far safer procedure in the presence of neoplasms or trauma and when uterine tamponade fails to check the hemorrhage. Blood plasma and parenteral fluids are lifesaving if given in sufficient amounts sufficiently early.

Uterine Rupture

Rupture of the uterus may occur in a natural labor which ends spontaneously as a result of tumultuous contractions. It may be induced by a scar in the uterus, the result of a previous cesarean section, or an incomplete rupture in a previous difficult labor which went unrecognized. The danger of uterine rupture following cesarean section is real, although the incidence has been greatly reduced since the advent of the low or cervical cesarean section. It is for this reason that our clinic rarely considers delivery from below after cesarean section justifiable and, with rare exceptions, follows the dictum "once a cesarean always a cesarean." Uterine rupture most often occurs as a result of difficult operative procedures, notoriously version and extraction. This operation, carried out in the patient who has been in labor a long time in a uterus that does not relax completely, carries considerable hazard for the mother as well as for the baby. Lastly, it must not be forgotten that many uterine ruptures in the country at large are the result of the ill-advised use of oxytocic drugs to improve the quality of the uterine contractions, or to hasten delivery when progress is slow. Most authorities feel that the unwarranted use of pituitary extract prior to the delivery of the baby is the most important cause of serious trauma to the reproductive tract.

During the thirteen and one-half years covered by this report there were 30 instances of rupture of the uterus, an incidence of 0.06 per cent. Seven of these women died, resulting in the high mortality of 23.3 per cent (Table VII). A more important consideration is the fact that the deaths in at least four of these seven women could have been prevented by better obstetrics and more energetic management after the accident.

TABLE VII. RUPTURE OF UTERUS

PATIENT	ETIOLOGY	CAUSE OF DEATH	AUTOPSY
B.	Brow presentation; version and extraction	Hemorrhage	No
M.	Pre-eclampsia; bag induction; transverse presentation; version and extraction	Hemorrhage	Yes
S.	Transverse presentation; version and extraction	Sepsis	Yes
P.	Abruptio placentae; Braxton-Hicks' version	Hemorrhage	No
M.	Intrapartum infection; craniotomy and extraction	Hemorrhage	Yes
L.	Pre-eclampsia; medical induction of labor; spontaneous rupture	Hemorrhage	Yes
W.	Spontaneous rupture	Pulmonary embolism	No

In four of these patients the rupture occurred following version and extraction, and in the fifth, during a difficult craniotomy. Although a number of ruptures followed previous cesarean sections, none of these women succumbed. Version and extraction is most often indicated in transverse presentations, deflexed attitudes of the head, and in prolapse of the umbilical cord. Properly carried out, it may be a lifesaving operation for the mother and her baby; poorly managed, it may prove disastrous.

Our fatalities inspire several well-known suggestions to increase the safety of this indicated procedure.

1. Transverse presentations must be recognized early before the rupture of the bag of waters, the impaction of the shoulder, and the development of uterine tetany.

2. Complete dilatation of the cervix must be present before any extraction can be safely carried out.

3. Complete relaxation of the uterus, which can be obtained with drop ether or chloroform only, must be present before any manipulations begin.

4. The early recognition of incomplete and complete rupture will be aided by the prompt exploration of the reproductive tract following difficult deliveries, particularly version and extraction, as well as in all cases of uncontrolled postpartum bleeding.

5. If uterine rupture has occurred, the rapid replacement of blood and plasma in ample amounts, and immediate hysterectomy will improve our mortality.

Heart Disease

Unlike the maternal mortality statistics for the country at large, heart disease shares the second place with hemorrhage as one of the three most important causes of maternal deaths. It was the primary factor in 13 cases, and an important contributory factor in at least four others. Heart disease has now entered the limelight with the time-honored trio—infection, toxemias, and hemorrhage—as a major cause of maternal mortality.

The increase in deaths from cardiac disease may be more apparent than real. The tremendous reduction in maternal mortality involved the more readily preventable causes such as death from infection, hemorrhage, and the toxemias. The incidence of heart disease has not decreased, nor has the maternal

mortality from this complication been reduced, so that it continues as a real hazard in pregnancy. Obviously, any radical improvement must come in the prevention of heart disease rather in its management during the gestation. Nevertheless, the large number of deaths ascribed to this cause must focus our attention on the obstetric management of the cardiac.

The incidence of heart disease in the obstetric services varies from 1 to 4 per cent of all admissions, depending on the locality. In about 95 per cent of these patients it is rheumatic in origin. Pregnancy is a serious hazard to the cardiac because of physiologic changes in the circulation induced by the pregnancy. Stander has demonstrated that the cardiac output begins to rise at the fourth month and increases steadily until near term, reaching an increase of 50 per cent over the normal. It returns to the previous level by the end of the third week postpartum. This increased circulatory load may be sufficient to provoke a break in compensation and its dire effects.

TABLE VIII

CARDIAC DISEASE	
Rheumatic heart disease	10
Mitral stenosis 9	
Heart failure—hypertensive disease	1
Auricular fibrillation—cause?	1
Heart failure—acute decompensation	1
PARITY	
Multiparas	9
Primiparas	4
LENGTH OF GESTATION	
24-36 weeks	7
36-38 weeks	2
Term	2
MODE OF DELIVERY	
Spontaneous delivery	7
Outlet forceps	2
Cesarean	2
Undelivered	2

The lesion is important, but may not be the determining factor in the prognosis of cardiac disease in pregnancy. Hamilton believes that mitral stenosis is the most serious pathology. However, the response of the cardiac muscle to the increasing demands is a better guide. In Table VIII it will be noted that in at least 10 of the 13 women who died of heart disease in our study it was of rheumatic origin, and in 9 of these mitral stenosis was the pertinent pathology. Only 2 of the 13 women reached term, and 7 died sometime between their twenty-fourth and thirty-sixth week of their pregnancies. These cases demonstrate the important fact that the serious cardiac patient may succumb any time after the fifth month, and that the delivery, regardless of the mode, may not affect the outcome (two of these patients died undelivered) or may serve only as "the straw that broke the camel's back."

Parity is not an important factor, for nine of these patients were multiparas. The older patient with rheumatic heart disease may have used up her cardiac reserve during the vicissitudes of life. The average length of life in these women

without regard to pregnancy is 40 or 45 years. Thus, a pregnancy in the late thirties may carry a greater risk than in the early reproductive years.

The management of the obstetric patient with heart disease is the most important factor in the ultimate outcome. In 4 of the 13 cardiac deaths, much of the responsibility for the dire outcome rests with the patient. One patient was advised in three different pregnancies that future childbearing was extremely hazardous, and something should be done to make this impossible. Three of the women first reported to the hospital in mid-pregnancy and in marked decompensation. Two of these had symptoms of decompensation for two and five months, respectively.

The physician erred in the conduct of 4 of the patients. In 2 patients a private physician was first aware of the gravity of the complication when they were admitted to the hospital with broken compensation. In 2 other patients who were followed in the outpatient department, the women were allowed to continue their usual activity until serious symptoms developed. Thus, in eight of the 13 cases the intelligent management of the patient by the physician, combined with her cooperation, may have resulted in a far better outcome.

The treatment of obstetric patients with heart disease has been fairly well standardized in our own and other large hospitals. Early diagnoses can be assured by urging patients to consult their physicians early in pregnancy as well as by a careful history (95 per cent have rheumatic heart disease) and complete physical examination. The cardiologist should see the patient to confirm the diagnosis and to evaluate the gravity of the lesion. In our clinic, the consultant follows the patient throughout pregnancy, delivery, and after her return home. It must not be forgotten that the postnatal period with is added physical and mental responsibilities represents a critical period in the life of the handicapped mother. Too often the obstetrician writes the patient off as a successful case when she walks out of the hospital, only to learn that the trials of motherhood are too great for her.

Patients who have been classified as class 1 and 2 cardiacs have no or slight limitation of their normal activity and are seen at frequent intervals during their gestation. They should be hospitalized if they develop fatigue, dyspnea, palpitation, or anginal pain on exertion. One or two weeks prior to term they should be brought into the hospital to await the onset of labor. Delivery can be accomplished by outlet or low forceps in order to spare the heart the additional load imposed upon it by the voluntary efforts associated with the second stage pains.

Class 3 patients have marked limitation of physical activity. Slight exertion will bring on dyspnea, palpitation, or anginal pain. These women should be hospitalized during any illness which may develop, such as an upper respiratory infection. They should be brought into the hospital at the first evidence of decompensation which may be pulmonary congestion. The last month of the pregnancy should be spent in the hospital. Carefully supervised bed rest is still the best cardiac stimulant, although the wisdom of absolute rest in bed has been questioned in the last year because of the increased hazard of thrombosis. The natural onset of labor should be awaited. Ample sedation during the labor

and the elimination of the second stage by low forceps delivery provides the greatest safeguards for the patient.

Class 4 cardiac patients are unable to carry on any physical activity without symptoms. Patients in this class, as well as in class 3, should not have children, for the risk involved is great. If they are seen in the first three months of the pregnancy, therapeutic abortion and sterilization is a justifiable procedure. Beyond this period, they should have long periods of bed rest in a hospital. Digitalis may be indicated for decompensation. If labor should ensue before complete compensation has been restored, delivery from below as described above yields the best results. Cesarean section at an elected time in the last month of the pregnancy should rarely be considered, and then only in the event the patient is thoroughly compensated.

Seven of the 13 patients in this series delivered spontaneously, and 2 were delivered by outlet forceps. Two of the patients died undelivered. Cesarean section on one of the two patients subjected to abdominal delivery was a questionable obstetric procedure and may have contributed to her death. The important lesson to be learned from this small group is that the medical management of the cardiac patient is the most important phase of her obstetric care.

Toxemia

The causes of the toxemias of pregnancy are not known, so that they cannot be prevented. Intelligent prenatal care and the medical management of the nonconvulsive toxemias will prevent the occurrence of eclampsia. This is extremely important, for the mortality of the convulsive toxemias is eighty times as great as the nonconvulsive.

The incidence of the nonconvulsive toxemias during the period covered by the report was 7.4 per cent of all deliveries. During this time 86 patients were treated for eclampsia. Thus the frequency of the latter was 0.018 per cent. The toxemias of pregnancy were directly responsible for 6 deaths, although 23 of the 81 patients who died had symptoms and findings of toxemia. (Table IX).

TABLE IX. TOXEMIA

	INCIDENCE (%)	NO. OF CASES	DEATHS	MORTALITY (%)
Nonconvulsive	7.4	3,435	2	0.058
Convulsive	0.018	86	4	4.6
Primary cause of death			6	
Contributory cause of death			23	

In some of these patients the toxemia contributed greatly to the fatal outcome. The patient who had an induced labor and a difficult delivery may have died of infection. However, it was the toxemia that made obstetric intervention necessary. Four of the six women who died had eclampsia clinically, and the pertinent pathology was demonstrated at the postmortem examination.

Fatalities are largely preventable in the management of the toxemias of pregnancy. The value of intelligent prenatal care is no better emphasized than in this small group of deaths. Five of the six patients had no prenatal care or,

what is equally bad, inadequate prenatal care. The early interruption of pregnancy was advised but refused in one patient. In another woman sterilization had been advised in two pregnancies prior to the one which ended fatally.

The management of the toxemias of pregnancy involves simple rules. Intelligent prenatal care will decrease the hazard of pre-eclampsia. Patients who gain excessively, who develop edema, albuminuria, and hypertension must be treated with the utmost care. Medical management does not cure these toxemias, but it will arrest the process or slow the progress until such time as labor will start spontaneously or it can be started by simple means. If the progress of the disease is not halted and if the patient develops findings as well as symptoms, the termination of the pregnancy becomes imperative. Delivery through the pelvis should be contemplated if at all possible, but if conditions do not warrant the induction of labor because of a long, uneffaced cervix or an inadequate pelvis, abdominal delivery is indicated. The success achieved in the treatment of the toxemias of pregnancy is in no small measure due to the prevention of eclampsia by terminating the gestation in the nonconvulsive state.

The treatment of eclampsia involves the medical management of this toxemia primarily. Adequate sedation, the establishment of good kidney function with the aid of hypertonic glucose solutions, and the induction of labor by the rupture of the membranes will suffice in all but the very serious patients. Delivery from below after the initiation of a good diuresis offers the best results for the patient. Cesarean section is rarely indicated in eclampsia. This major surgical procedure increases the hazards of the convulsive toxemia. Dieckmann states that cesarean section under local anesthesia is justified in "the patient with the severe type of eclampsia with an uneffaced cervix after eight to twelve hours of proper medical care." Following these criteria this operation was performed in 12 of the 86 cases, an incidence of 14 per cent. In some, abdominal delivery was indicated because of cephalopelvic disproportion or the patient developed convulsions after cesarean section for pre-eclampsia.

Cesarean Section

Dieckmann recently presented an exhaustive review of the cesarean sections at the Chicago Lying-in Hospital and a brief résumé will suffice. Eleven of the eighty-one women who died were delivered by the abdominal route. At a superficial glance, it would appear that abdominal delivery comprising 12.3 per cent of the fatalities was a major factor in mortality. A careful perusal of Table X will reveal that in at least three of the cases the operation was performed entirely in the interest of the baby. In three other patients, inexperience of the surgeon was a major factor in the fatality, which can be charged to a teaching service. Two of the women with cardiac disease might have fared better by delivery by the vaginal route, but the gravity of their heart disease demonstrated clinically and at autopsy made any other outcome problematic.

Cesarean section in the hands of the specialist for carefully selected indications in the absence of contraindications need carry no great risk. The modern maternity with its expert personnel, the wide selection of anesthetic agents, carefully suited to each patient, the additional safeguards of the sul-

TABLE X. CESAREAN SECTION DEATHS

PATIENT		INDICATION	LIVED	TYPE OPERATION		CAUSE OF DEATH
1.	A	Tuberculous meningitis	11 days	Lap. trach.	(A)	Tuberculous meningitis
2.	G	Tuberculous meningitis	4 hr.	Classic		Tuberculous meningitis
3.	S	Contracted pelvis	25 hr.	Classic	(A)	Abdominal hemorrhage
4.	A	Myoma	9 days	Classic and myomectomy	(A)	Peritonitis
5.	D	Placenta previa	3 hr.	Lap. trach.	(A)	Exsanguination
6.	G	Cardiac disease	11 wk.	Lap. trach.	(A)	Peritonitis, acute endocarditis
7.	C	Cardiovascular-renal	17 hr.	Classic	(A)	Cardiac failure, anemia, chronic nephritis
8.	H	Placenta previa	16 days	Lap. trach.	(A)	Pulmonary embolism
9.	S	Disproportion, diabetes, inertia	10 days	Cesarean hysterectomy	(A)	Peritonitis
10.	L	Coma, hypertensive encephalopathy	26 hr.	Lap. trach.		Cerebral hemorrhage; eclampsia?
11.	H	Pre-eclampsia	29 days	Lap. trach.	(A)	Pulmonary embolism

(A): Autopsy.
Lap. trach.: Laparotrachelotomy.
A live baby was delivered in each case.

fonamides and penicillin, and the ready availability of blood and plasma in liberal amounts have helped to remove the unusual hazards of abdominal delivery. The maternal mortality from this operative intervention should truly be the irreducible minimum. Why is it then that Dieckmann reports that cesarean section still carries a mortality of 2 to 5 per cent in the large clinics and perhaps twice that in the country at large? The answer is to be found in the selection of patients for abdominal delivery. The contraindications to the operation are far more important than the indications.

The safest time to do a cesarean is before the patient goes into labor as an elective procedure, or after a carefully conducted test of labor of less than twenty-four hours. Prolonged labor, repeated vaginal examinations, rupture of the membranes longer than twenty-four hours, manipulation, all add to the risk of abdominal delivery. Cesarean section as a way out of difficulty in the patient who fails to make progress after several days of labor and following many examinations, is a hazardous procedure and rarely justified. The criticism that too many cesareans are performed in this country is a valid one, but even greater criticism should be leveled at the fact that too few are done at the right time.

During the period covered by this report, 1,824 cesarean operations were performed at the Chicago Lying-in Hospital. Most of these, 1,704, or 93 per cent, were of the low or cervical type; 98 were Porro cesarean sections; 22 were of the classic type. Cesarean section was the method of delivery in 3.9 per cent of all patients, or less than one in twenty-five. The mortality in all cesareans was 0.6 per cent, but in the low or cervical type, laparotrachelotomy, it was 0.35 per cent.

Anesthesia

Some form of anesthesia is necessary for the majority of hospital deliveries. The anesthetic may play a major role in the conduct of delivery. Anesthesia has become an important medical specialty, and as much care should enter into the

choice and administration of the anesthetic as in the operative procedure. Until the present emergency, all anesthetics were administered by specially trained physicians.

There were two anesthetic deaths in the present series. One woman died during the operation, and the other within twenty-four hours of bronchopneumonia. During this period, over 50,000 anesthetics were administered. Although the mortality was not high, these were preventable deaths. During the same period there were some forty-five instances of aspiration of material into the lungs during an inhalation anesthetic, and eight patients were seriously ill, but recovered. Special measures should be instituted to prevent the aspiration of food and foreign material into the lungs at the time of delivery. Patients in labor should not receive solid food. In spite of this safeguard, a patient is often put to sleep immediately after a hearty meal and serious vomiting results.

All anesthetic agents carry some risk for the mother and the baby. This risk becomes negligible when the anesthetic is carefully chosen and administered by trained personnel. Inhalation anesthetics were most commonly used for vaginal deliveries, and consisted of ethylene or cylopropane and oxygen, with or without ether. Drop ether was used rarely and chloroform not at all. Local anesthesia is the safest anesthetic agent and is ideal for cesarean section. At least three of every four ceareans were done successfully under local infiltration anesthesia. Recently caudal has been used in a restricted number of cases. No spinal anesthesia was used in obstetrics.

Embolism

Pulmonary embolism as a cause of death is rare, but it accounted for six deaths, an incidence of 0.012 per cent. It will be noted in Table XI that in three of the patients there were no clinical indications of thrombosis prior to the fatal accident, nor were there any evidences of infection during the postpartum period and at autopsy examination. Death followed rapidly after the first clinical manifestations of massive pulmonary embolism.

Infection was the major factor in the causation of the remaining three deaths. Two of the women were subjected to cesarean section and one to hysterectomy following uterine rupture. In all three, pelvic vein thrombosis was

TABLE XI. EMBOLISM

CLINICAL DIAGNOSIS	DELIVERY	POSTPARTUM COURSE	DAY OF DEATH
Normal pregnancy, term	Spontaneous	Normal	1
Normal pregnancy, term	Low forceps; episiotomy	Normal	8
Normal pregnancy, term	Outlet forceps; episiotomy	Normal	10
Severe pre-eclampsia	Laparotrachelotomy	Septic course; pulmonary infarcts	29
Placenta previa	Laparotrachelotomy	Septic; septic pulmonary infarcts	16
Prolonged labor; spontaneous rupture of uterus	Hysterectomy	Septic; stormy; septic pulmonary infarcts; emboli	12

probably induced by infection and was the source of septic emboli to distant foci. These women had warning pulmonary infarcts evidenced by chest pain, pleural effusions, râles, and x-ray findings prior to the fatal massive embolus.

The prevention of uncomplicated pulmonary embolism has been the subject of much clinical investigation recently. Bed rest has been seriously indicted as the most important single cause of embolism. It has been demonstrated that rest in bed favors the development of thrombi in the deep veins of the lower extremities which ultimately may serve as emboli. Some clinicans have urged the elimination of unrestricted bed rest as far as this is compatible with therapy. Patients are allowed out of bed the second or third day after delivery and after major abdominal operations. It is likely that the pendulum has swung too far and that restricted bed rest and moderate activity may offer the greatest aids to recovery as well as the greatest safeguards in the prevention of thrombosis. It has been the policy of the Chicago Lying-in Hospital to refrain from such complete sedation that the patient lies comatose for hours at a time without moving the extremities. Free movement in bed is insisted upon immediately after delivery, and exercises are instituted at an early date. Although normal patients are kept in bed for about eight or nine days, the active puerperal regime prevents stasis of the circulation.

Thrombophlebitis, which is the result of infection, can be prevented by all the measures promulgated for the prevention of infection. The careful selection of patients for cesarean section, care to prevent trauma and infection at the time of delivery, and better obstetrics will help to minimize the danger of pelvic vein thrombosis. The patient with placenta previa who died of embolism might have survived if she had the cesarean operation at the time of her first vaginal examination, for virulent organisms may not have been present in the reproductive tract.

The role of anticoagulants such as heparin and dicoumarin in the treatment of thrombosis and embolism is still debatable. These drugs properly used may decrease the hazard of embolism in the patient who has had clinical manifestations of infarction or in whom a diagnosis of pelvic thrombophlebitis has been made. Surgical removal of massive pulmonary emboli are dramatic procedures, and few successful cases have been reported.

Transfusion Reactions

The timely administration of blood in adequate amounts is lifesaving, but incompatible blood can be death-dealing. Some of the patients who survive a reaction from the transfusion of incompatible blood sustain permanent renal damage. Three patients in this group of 81 deaths succumbed as a result of a transfusion reaction. In at least one and possibly two of the patients the Rh factor was involved.

Hemorrhage is such an important complication in pregnancy and labor that every patient should be typed as part of the prenatal care. An excessive loss of blood should be anticipated, and proper blood should be made available leisurely, when mistakes are less likely. All obstetric patients should have their Rh

determined, and the Rh- negative women should receive Rh-negative blood. This is particularly important if the patient is to have more than one transfusion, or if she has delivered a baby with evidences of erythroblastosis. The prompt and vigorous treatment of the patient who shows any signs of a transfusion reaction will improve the prognosis.

Conclusions

A summary of the maternal mortality at the new Chicago Lying-in Hospital during the last thirteen and one-half years is presented. The various causes are carefully analyzed and compared with the statistics for the country at large. Preventable factors were present in two of every three deaths. The management of the complications responsible for mortality at the institution are briefly summarized.

Discussion

DR. JAMES E. FITZGERALD.—The commendable results which Dr. Davis presents can be achieved only by the concerted effort of the staff of a well-organized hospital. For comparison let me tell you what happens in a charity hospital in which the patients are not selected or are not under the control of the members of the staff, such as the Cook County Hospital.

We delivered 45,557 patients with a total mortality of 0.31 per cent, which is almost twice as high as the percentage Dr. Davis presents. Those deaths are accounted for by the fact that many patients are admitted to a charity hospital with no prenatal care and frequently with inadequate care at delivery elsewhere. We accept responsibility for all deaths that occur in the hospital. Still, I think that our series compares favorably with his series, and we have much less supervision of the members of our active staff, who are usually residents and interns, than he has of his personnel at the Lying-in Hospital. I should like to comment on the statements made by Dr. Davis, that some improvement in the mortality during the last two years may be due to discontinuance of deliveries at home. This would be definite news to the founder of the institution and its biography in the public press. He says that only three women delivered at home in fifteen years died, so discontinuing the home service for two years had very little effect on the Lying-in maternal mortality.

In Dr. Davis' series he has as many deaths from heart disease as from toxemia. In the Cook County Hospital we have had only two deaths from heart disease in pregnancy during seventeen years in patients over whom we had complete control, and who went to our cardiac clinic for prenatal care. On the other hand, Dr. Davis finds that since the administration of the sulfonamides and penicillin the mortality from infection has decreased. At the Cook County Hospital the mortality from infection has not decreased since the advent of the sulfonamides and penicillin.

One other question that Dr. Davis brings up is the management of placenta previa, and he states that he is accustomed to make a diagnosis of placenta previa by pelvic examination. It has been increasingly our opinion in a large series of cases that we did as much harm in attempting to make a diagnosis of placenta previa by pelvic examination as we did when no diagnosis was made.

DR. JAMES A. GOUGH.—During the last five years at St. Luke's Hospital we have confined 6,000 women, or, approximately, 100 per month. In those 6,000 women there were 10 maternal deaths. During this same interval 267 abortions were cared for in our hospital and 43 ectopic pregnancies. There were no deaths from the ectopics. There was one death from a septic abortion, the patient admitted in coma and dying a few hours later.

Practically 60 per cent of our patients are private and 40 per cent are confined by the resident staff, and the mortality is distributed exactly in that proportion, six deaths among

the private patients and four in the dispensary service. Of these deaths, postmortem examinations were obtained on six, and in the four which were not posted the causes of death were sufficiently obvious to be unquestioned. The causes of death were as follows:

Pulmonary embolism	2
Atelectasis during cesarean section	1
Cardiac disease	1
Eclampsia	1
General peritonitis following cesarean section	1
Empyema	1
Pneumonia	1
Massive intracranial hemorrhage from rupture of the basal artery	1
Postpartum hemorrhage	1

Our incidence of maternal deaths is thus comparable to the series which Dr. Davis has reported, but we have taken advantage of the time element, and our report is based on the last five years only, while Dr. Davis' is based on thirteen years or more.

DR. LUELLA E. NADELHOFFER.—I thought you might be interested in a comparable period for the whole city of Chicago. Here, in 1944, in 60-odd hospitals there were 59,379 live births. Our mortality in Chicago has declined in the last thirteen or fourteen years. In 1931, the year in which Dr. Davis started, the mortality rate for Chicago was 46 per 10,000 live births, and for the United States as a whole 66 per 10,000 live births. In 1944 our provisional maternal mortality in Chicago was 16 per 10,000 live births, which is the lowest it has ever been. The latest we have for the United States was in 1942, when it was 25 per 10,000 live births.

It is difficult, as Dr. Gough said, to state comparable statistics over this long period of time, but the last year for which we analyzed the causes of death was in 1943, in which we had 128 maternal deaths. The chief causes were 20 from abortions, most of which were septic; 5 from ectopic pregnancy; 25 from hemorrhage; 30 from toxemia; 22 from infections, and 20 from other causes. The essential difference between these statistics and the ones presented by Dr. Davis is that he has no deaths from abortions. We still have many septic abortions which are admitted to other hospitals. There are more deaths from cesarean section in the city as a whole. The last time I went over the figures about one-fourth of the deaths followed cesarean section. There are more eclampsia deaths than in his series. I agree with Dr. Fitzgerald that septicemia is still a leading cause of death in Chicago. We included abortions with that.

In the Bulletin from the Metropolitan Life Insurance Company in August, 1944, it was stated that a large number of maternal deaths are preventable. Septicemia is still the greatest cause in their series of 2,800 deaths. The Sub-Committee on Maternal Mortality of the Joint Maternal Welfare Committee of Cook County, of which Dr. Baer is Chairman, feels that one of the chief aims should be against abortion deaths. We do not know just what can be done about these. It is largely a local problem. The medical profession should perhaps lead the way in trying to find a means of preventing these deaths from septic abortion.

We feel in Chicago that timely and adequate consultation is a factor in the prevention of some of these maternal deaths, especially in the smaller hospitals.

In Dr. Davis' statistics, there were a number of cases in which hemorrhage was mentioned. I believe that is one of the most important causes of maternal deaths before our Sub-Committee on Maternal Mortality. Again and again the Committee says that adequate blood replacement was not given. In a hospital staff meeting which I attended on Wednesday, it was suggested, that in cases of placenta previa, not only one flask of blood should be given but two, three, or four. That is possible in a hospital where there is a blood bank, but in the majority of smaller hospitals it is not possible to have this blood available. We believe that some method whereby hospitals can get blood replacement easily, cheaply, and promptly is very important. The Joint Maternal Welfare Committee has been working with some outstanding hematologists in the city and they are planning to institute a program whereby plasma and resuspended red blood cells will be available in the city of Chicago.

DR. EDWARD ALLEN.—Are we justified in our teaching of obstetrics in talking about the irreducible minimum? When we compare the results of the private service, the house clinic service, and the outpatient service, we find a marked difference both in the mortality and the morbidity rate. The operative incidence on the house teaching service is about ten times as great as that of the outpatient service. I realize fully that we must teach some operative obstetrics to students, but perhaps our teaching would get better results if our house operative incidence were more nearly that of the outpatient service.

The prime interest of the obstetric patient is safety to herself and baby, and secondarily, the relief of pain. I believe a warning should be sounded in the teaching of students concerning the increased mortality and morbidity which perhaps may result from the obstetrician's attempts to relieve all pain during childbirth.

DR. H. W. SHUTTER.—In Milwaukee we opened the Milwaukee Hospital and proceeded to get fine statistics. We delivered 4,300 women without a death, and then we had 4 deaths in the next 800 deliveries.

We have had some enthusiastic users of caudal anesthesia, and we have had two deaths. The second one died in thirty minutes from the time injection was started. Since then we have cut down caudal anesthesia to cases where it is really indicated.

DR. EUGENE A. EDWARDS.—The highest incidence of death is due to infections following abortion. I would like to see cooperation between the City Health Department, the State, and the medical profession to reduce the incidence of abortion. The highest incidence of infection follows abortion. I believe this can be reduced. I would like to see cooperation between the State Health Departments, and the medical profession in punishing the abortionist.

DR. DAVIS (Closing).—The only question that I wish to answer is the one raised by Dr. Allen. We are all agreed that the safest way for the normal woman to have her baby is to deliver as naturally as possible. If all pregnant women were carefully screened and those with complications were confined in a well-conducted maternity, the others could be delivered at home safely. However, women prefer to be delivered in hospitals. They demand the benefits of analgesia and anesthesia. These refinements of obstetrics necessarily increase the incidence of operative deliveries and the complications of the third stage. Everything possible must be done to safeguard obstetrics in our hospitals, for these institutions are the logical places for women during childbirth.

Home delivery services are slowly disappearing, and it will not be long before most of the women will be confined in hospitals. In the urban centers few births occur in the homes. In the country at large, there has been an increase of 27 per cent in the hospital births in the last five years. During the last year almost 70 per cent of all babies born in the United States were delivered in hospitals. Our present task is to promote greater safeguards for hospital deliveries so that every patient can be delivered safely in a hospital by a competent physician.

THE EVOLUTION OF THE BIOLOGIC CONCEPT OF THE ETIOLOGY OF LATE TOXEMIA

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THE Renaissance of obstetrics and its elevation from an almost exclusive interest in mechanical aspects to the rank of a science is primarily due to a succession of constructive advances made in this century along the avenues of biologic investigation. They paved the way for a realistic coordinated approach to the intricate problem of toxemia and played a telling part in providing a reasonable explanation for its basic mechanism. In contrast with the melancholy iteration in the course of discussions upon the etiology of the late toxemia to the effect that most of the stream of research effort has been losing itself in the sand, recent orientation takes the position that the answer no longer eludes us.

Ideas seldom spring full-fledged from the mind of man. It will be profitable to trace the excursions made in planned biologic researches into hitherto untrodden fields. The integration of an array of newly acquired fundamental facts into a coherently unified concept of toxemia, although sharply at variance with the traditional trend of thought, marks the harvest of investigations spanning the range of four decades in this sphere. The detailed study of the histology and function of the chorionic villi of the human placenta revealed among other hitherto unknown features the occurrence at any stage of gestation of syncytial buds which project into the surrounding maternal blood spaces, gradually detach themselves and finally dissolve in the maternal blood stream. The remarkable vital activity of these syncytial derivatives was discernible in specifically stained microscopic specimens. Experimental evidence shows that these fragments act as a powerful formative stimulus to various maternal ductless glands which respond with hyperplastic changes. The chromophobe hyperplasia known to occur during pregnancy in the anterior pituitary gland was obtained by various investigators with the administration to experimental animals of estrogens (Berblinger, Vasquez-Lopez). However, the distintegration of these syncytial elements represents an important source of protein split products, histamine-like substances. The biologic significance of this event becomes immediately apparent if it is remembered that the shedding of syncytial buds occurs from a chorionic surface which at term measures 6.5 square meters. Foremost among the maternal organs involved in the damage sustained by the abundance in the blood of such protein split products is the liver which both by specific function tests and in microchemical stains revealed glycogen deficiency as the principal biologic deviation. In my original communication (Arch. f. Gynaek., 1909) as well as in a more extended discussion (AM. J. OBST. & GYNEC. **26**: 311, 1933) the bearing of this phenomenon on certain derangements of metabolism during gestation was detailed. There are quoted interesting and informative facts concerning hepatic lability during the second half of normal gestation in forty out of a hundred apparently normal cases and definite in-

sufficiency of liver function in toxemia. Of more recent date is the recognition of the significance of the syncytial fragments as implements of conveyance into the maternal circulation of certain hormonal and chemical substances which are normally stored in large quantities within the human placenta (sex hormones, acetylcholine). The selective action of the chorionic epithelium in the assimilation and placental transmission of the requisite material for fetal nutrition was fully detailed in my monograph *Biology of the Human Placenta* (1905), and has since received universal recognition, while the view which tended to relegate to the placenta the function of merely a semipermeable membrane is losing favor.

The introduction of posterior pituitary extract in 1911 for the initiation of rhythmic uterine contractions in the first and second stages of labor and for the induction of labor aroused interest in other pharmacologic properties of the preparation. In consequence, clinical observations and experimental premises joined in favoring the view of a posterior hypophyseal-cortico adrenal mechanism underlying late toxemia (Zentralbl. f. Gynäk., 1918). The announcement stimulated a prodigious amount of work and debate as summarized in a paper "Recent Advances in the Study of the Etiology of Eclampsia." Proceeding from the remarkable identity of the chemical findings in the blood of eclamptics and of laboratory animals which had received intravenously postpituitary extracts, the accumulated pertinent experimental and microscopic data obtained by various investigators concerning the nature of late toxemia were collated. The concept of an undue pitressin effect as the basic factor involved was advanced (Am. J. Obst. & Gynec. **26**: 311, 1933).

The result of extensive experimental studies concerned with the intravenous administration of *histamine* to pregnant and nonpregnant animals (carnivora) served to contribute to the understanding of the etiology of the toxic type of premature separation of the normally implanted placenta (Am. J. Obst. & Gynec. **12**: 159, 1926). Recent significant data tend to clinch the argument that the condition virtually represents a histamine effect. In the wake of the discovery of histaminase in the human placenta (Danforth, D. N.: Am. J. Physiol. **119**: 294, 1937) Marcou, Effkemann, Stern, Werk, Zeller, and Ahlmark reported that during normal gestation the blood invariably shows an extraordinarily high activity in destroying histamine. This phenomenon is specific and does not occur in any other condition. The activity of histaminase was found diminished in severe pre-eclampsia and particularly low in premature separation of the placenta. As a corollary, the blood level of histamine and histamine-like substances in the latter condition appeared fifty times higher than normal (L. Cusmano, Ginecologia **7**: 285, 1941, rev. in Chem. Abstracts, 1945, p. 3353). The inference concerning the true nature of the condition under consideration seems inescapable. In consequence, the administration of adrenal cortex preparations which are known to antagonize histamine, and of blood transfusions, as well as the abandonment of ether anesthesia in the treatment of the toxic type of premature separation of the placenta, as suggested in the communication mentioned above have proved their therapeutic value.

Coordination of data concerning certain well-defined pharmacologic principles represents an integral part of the recently advanced reorientation on the etiology of late toxemia (West. J. Surg. **49**: 615, 1941; Cincinnati J. Med. **23**: 107, 1942; Am. J. Surg. **45**: 361, 1944). While in the past the placenta was generally considered the chief characteristic of the pregnant state and, in toxemia, the principal factor responsible for the elaboration of "toxins," the new tenet inclines to the view that the pregnant state is essentially conditioned by the altered basic endocrine pattern. Notable among the hyperplastic changes occurring in the ductless glands during pregnancy are the phenomena in the adrenal cortex, the thyroid and the anterior hypophysis. In the present discussions the demonstration of increased secretion of the basophiles during the last trimester of normal gestation and of cortical structures had first call in view of clinical evidence obtained in recent years that the adrenal cortex as well as the pituitary basophiles may have pressure potentialities (G. A. Perera, J. A. M. A. **129**: 537, 1945). These facts, in conjunction with augmented reactivity of the arterioles to pitressin as the result of the presence during pregnancy in the blood of placental sex hormones in concentrations far above anything occurring in the nonpregnant state, served as the basis for the appreciation of a delicately adjusted equilibrium during normal gestation between the opposing tendencies on the blood pressure of certain endocrine factors and placental acetylcholine. A disturbance of this balance in toxemia was demonstrated by our report of remarkably low acetylcholine values in 28 placentas and by the unequivocal evidence adduced by Mukherjee of increased concentration in the blood of postpituitary principles in toxemia (J. Obst. & Gynaec. Brit. Emp. **48**: 586, 1941). In addition, as quoted in my papers, cholinesterase activity in the toxemic placenta was found to be significantly higher than in normal conditions. This fact was recently fully confirmed by the studies of Woodbury (J. A. M. A. **128**: 585, 1945). Exposition of functional aberrations of the placental enzyme systems, implied here and recorded above relative to the discussion on histaminase, attains significance in the light of recent work which tends to illustrate the influence of the hormones of the adrenal cortex, the pituitary, and the thyroid on the enzymic activities of various organs. The presence in the toxemic placenta of widespread areas of disintegration, occasionally only discernible on microscopic study (J. Young), has been generally accepted as an item of important information. The interrelation of these acute placental lesions to the occurrence of increased cholinesterase with rapid destruction of placental acetylcholine is apparent. Experimental evidence adduced by Hartmann demonstrating that prolonged spasm of the umbilical vessels may be elicited by histamine or by postpituitary pressure principles (1930) serves to throw light on the mode of formation of the red infarcts in the toxemic placenta, while the view that toxemia is produced by the absorption of protein split products from the infarcted area (tyramine, guanidine) is not supported by any evidence.

To the previously noted facts along clinical, experimental, morphologic, and chemical avenues quoted in favor of the concept of undue effects of the pituitary pressor principle as the unifying factor in the analysis of the man-

ifestations of late toxemia has recently been added the demonstration by Stehle and Bourne of the blood concentrating effect and of the phosphorus raising action of the pressor hormone (J. Physiol. **64**: 229, 1943) in gratifying accord with factual data in toxemia. Such evidence is eloquent. There is indeed reason to regard the analogy complete when it is recalled that anoxia of the tissues as a fundamental aspect of toxemia also occurs consequent upon the intravenous administration to unanesthetized dogs of pitressin (Grollman, Geiling).

Critical analysis of the objections raised by L. Dexter and his associates to the significance of pitressin as an etiological factor revealed that they are unsubstantiated (J. A. M. A. **122**: 892, 1943). Indeed, the recent investigations of Sawyer and Ettinger conclusively demonstrated in dogs the blood pressure raising property of posterior pituitary extracts in conformity with former observations recorded by Leimdoerfer, Keith, and Griffith (Canad. J. Research **22**: 26, 1944). In this discourse, it is worthy of note that quite recently another link has been added to the chain of evidence pointing to the fundamental part played by the pituitary in the disorder under consideration. Conglomeration in the anterior pituitary lobe of basophiles in discreet foci in eclamptics, as first described by Berblinger, has been recently observed in the large majority of cases studied by other investigators. These findings may have a bearing on the occurrence of a high gonadotropic content of the serum in toxemia. In the light of recent evidence which indicates a distinct relation of the basophiles to hypertension and to hyperplastic changes in the adrenal cortex, these observations may be significant.

Dieckmann and Michel (1937), and Schockaert and Lambillon (1937), working independently, showed that pre-eclampsia is characterized by a marked degree of hypersensitivity to injected vasopressin. With normal gestation exhibiting a state of refractoriness to vasopressin, it seemed necessary to postulate an inhibitory factor which under normal conditions holds the sensitizing effect of estrin on the arteries in check and is lacking in toxemia. Kustner, Obata, Byrom, DeValera, and Keller likewise predicated an inhibitory agent in normal gestation. Investigators who recently reported that hypertensive pregnant animals commonly develop a well-marked decline in blood pressure during the last part of pregnancy believe that this phenomenon occurs because the placenta forms some antipressor substance. Being a powerful vasodilator acetylcholine, significantly constant both as to presence and remarkable concentration in the normal placenta suggests itself as the substance provided by Nature for the neutralization of the effects on the hyperreactive arteriolar tree of vasopressin and of certain overactive hormonal products (adrenal cortex, thyroid). The recent experimental demonstration of an antagonistic pharmacodynamic action on the vasomotor mechanism of the pituitary pressor principle and acetylcholine (1941) bears on the existence during normal gestation of a delicately balanced blood pressure regulating mechanism. Dislocation of this equilibrium in toxemia as the result of impaired destruction of pitressin in the functionally deficient liver and choline deficiency in the placenta and the blood, with the resulting inadequately opposed effects of naturally secreted postpituitary pressor principles, may be regarded as the keystone to the interpretation of the diverse manifestations of

late toxemia, a morbid degree of generalized vascular spasm, tissue anoxemia, and derangement of water and carbohydrate metabolism constituting the essential sequela. In our concept, to the placenta is accorded merely the role of the determining factor in initiating and sustaining the increased activity of the adrenal cortex, the thyroid, and pituitary gland.

The present view broadens into a larger conception of the complex mechanism concerned in the causation of late toxemia. If examined with an open mind and discriminating balance, it requires no special prophecy to recognize that we stand at the threshold of the conquest of the disorder. The burden of proof must be with those in disagreement to the views advanced.

Disease, if it is to be understood, must be interpreted in physiologic terms, while rational therapy depends upon the basic comprehension of the cause of the disorder in question. In previous communications on the subject, among the cardinal aspects which enter into the therapy of toxemia the preservation as far as possible of the functional integrity of the liver as the organ most concerned with the control of the endocrine secretions of pitressin and thyroxine and of glycogen was stressed. To this end, in addition to the proper diet, the administration in the prenatal period of an adequate supply of vitamins B and C and of calcium, which exercises a protective power in relation to the liver, was suggested.

As indicated in a previous paper, sedatives (morphine, barbiturates, magnesium sulfate) exert a controlling influence over the effects of postpituitary principles on the midbrain. The significance of these facts is evident in the light of the demonstration by Verney, Danilov, Chang, and Lim, that painful stimuli of the splanchnic nerves cause an increase in the output of the hormones of both the posterior pituitary and the adrenal cortex.

A PARAVESICAL EXTRAPERITONEAL CESAREAN SECTION TECHNIQUE

With an Analysis of 160 Paravesical Extraperitoneal Cesarean Sections

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THAT there still occurs, especially in the larger obstetric services, problems which can best be managed by recourse to an extraperitoneal cesarean section is a fact more or less generally conceded. All too frequently one finds a patient long in labor, with a live baby, presenting part unengaged, or only fixed at the inlet, membranes ruptured for many hours, and perhaps frankly or at least potentially infected, and in whom delivery through the birth canal with a satisfactory result for both mother and child is not to be expected. These patients truly present a serious problem for adequate and satisfactory obstetric management.

In managing this type of problem, we feel that the best results may be obtained by utilizing an extraperitoneal approach to the lower uterine segment and thus effecting delivery by cesarean section without invading the peritoneal cavity.

The more widespread use of extraperitoneal cesarean section has been retarded by one or more of a variety of objections raised against the operation. Most frequently heard are: (1) the technical difficulties encountered in the performance of the operation; (2) the need for far more than ordinary operative skill for its adequate performance; (3) the relative infrequency with which one finds a true need for the operation; (4) the possibility of opening the peritoneum and thus defeating the purpose of the operation; and (5) danger of injury to either or both the ureter and the bladder.

We are presenting here a paravesical extraperitoneal cesarean section technique which in our hands has served well; the various steps of the operation are deemed to be not too difficult technically. It does not demand a degree of surgical competency over and beyond that possessed by the average obstetric surgeon; and its various steps can be mastered with an occasional case, and the relative infrequency with which one is called upon to utilize the procedure need offer no serious objection to its use.

We are analyzing 160 paravesical extraperitoneal cesarean section techniques performed at the Margaret Hague Maternity Hospital with particular reference to objections (4) and (5), and offer in addition an operative technique which we think obviates the other objections set forth above.

The first extraperitoneal cesarean section at the Margaret Hague Maternity Hospital was done Dec. 26, 1931, by Dr. Samuel A. Cosgrove. The technique as originally set forth by Latzko was followed. In August of 1932, Burns[1]

operated on the fourth case at the hospital and demonstrated the technique described by him of utilizing a paravesical approach to the lower uterine segment. In the group of cases here analyzed, the only one constant technical factor is the paravesical approach to the lower uterine segment. The technique here presented is the result of many modifications, deviations, and evolutions from various points in the techniques already set forth. Simply stated, it is a paravesical approach to the retrovesical area of the lower uterine segment and an enlargement of this area to obtain adequate exposure for delivery of the baby, all the time remaining infraperitoneal (i.e., below the posterior fold of peritoneum). Nothing of an original nature is claimed for the methods described in this presentation. It represents what we consider to be improvements in the already described techniques, which improvements stem from a clearer and more definite knowledge of the anatomy of the various layers of the pelvic fascia and the duplications and reflections of the pelvic peritoneum, together with an excellent opportunity to test many variations from the already described and established procedures until we obtained what we consider to be a technique which has proved to be simple, adequate, and satisfactory. Multiple variations and improvements from the procedure here set forth fall well within the scope of any competent surgeon.

For the adequate understanding of an extraperitoneal approach to the lower uterine segment, accurate knowledge of the anatomy of the pelvic fascia and the relationship and reflections of the various layers of peritoneum is of primary importance. We do not feel that it falls within the scope of this paper to detail the anatomy. It is better said elsewhere.[2]

While the operation when properly performed is de facto truly an extraperitoneal undertaking, it seems to us that the rationale and anatomic basis of the entire procedure may be better understood and its technical performance more easily mastered if the two main steps so necessary for its proper completion were more emphasized, viz., a retrovesical infraperitoneal exposure of the lower uterine segment. These two concepts of retrovesical and infraperitoneal constitute the basis for the proper management of the entire operation.

The procedure here developed concerns itself with three distinct steps:

1. Paravesical approach to the retrovesical area of the lower uterine segment.

2. Identification of the infraperitoneal portion of this retrovesical area of the lower uterine segment.

3. The infraperitoneal enlargement of this area.

Technique

General preparation.—Anesthesia as elected: usually 100 mg. spinal novocain. (1) Vaginal preparation and examination. (2) Insertion of retention catheter into bladder. Two hundred cubic centimeters of colored solution run in and tested for ease of flow out. Use 1.6 per cent indigo carmine (one 5 c.c. ampule of 0.8 per cent/1000 c.c. distilled water). (3) Abdominal preparation.

I. Approach to the Retrovesical Area of Lower Uterine Segment

(4) Left paramedian incision through skin from above distended bladder, down to symphysis: expose and incise anterior sheath of left rectus. (5) Rectus muscle is separated

by blunt dissection from the underlying transversalis fascia, and then lifted upward and retracted laterally. (6) Visualize large vessel (deep epigastric) which runs parallel to the rectus. (7) Identify at upper part of left lateral surface of bladder (the left paravesical space) an area of chicken yellow fatty tissue (Fig. 1). (8) Insinuate index and second finger into the left paravesical space in region of the chicken yellow fat and lift from the underlying bladder the transversalis fascia and the anterior sheath of perivesical fascia. Incise these layers of fascias and extend the incision well over beyond the midline of bladder. This incision of fascia should be directed downward in order to avoid injury to the anterior peritoneal fold at top of bladder. These two layers of fascia may come off singly or in layers—if singly, repeat procedure until bladder muscle is exposed (Fig. 2). (9) Partially empty bladder. (10) Return to the left lateral surface of the bladder and with finger dissection started in the left paravesical space along the left surface of the bladder, begin removing the bladder from the underlying lower uterine segment.

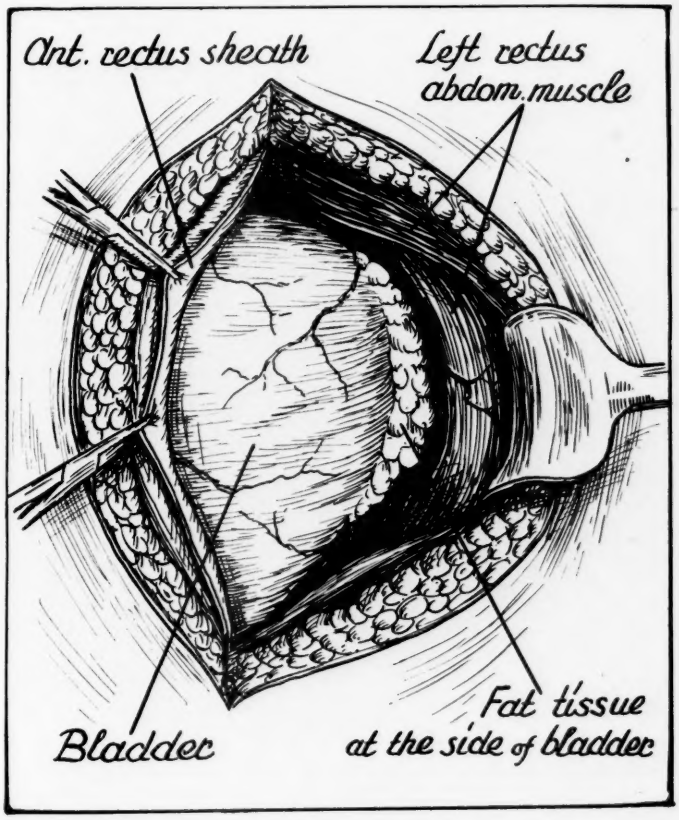

Fig. 1.—Area of "chicken yellow" fat tissue at the side of distended bladder; the left rectus abdominus muscle must be retracted upward and laterally for proper exposure of this area.

II. Identification of Exposed Retrovesical Infraperitoneal Area of the Lower Uterine Segment

(11) After the bladder is but partially removed there will be exposed a triangular area on the anterior surface of the lower uterine segment. The upper border of this triangle is formed by the posterior peritoneal fold; the lower mesial border by the partially removed bladder; the lateral border by the parieties (Fig. 3).

III. The Infraperitoneal Enlargement of the Retrovesical Area

(12) Incise the fascia in this bared triangular space. This is the posterior sheath of the paravesical fascia and the anterior sheath of the periuterine fascia. (13) With Richardson retractor, retract the posterior peritoneal fold upward, the bladder downward to the right, and the fascia laterally to the left. This retraction of posterior peritoneal fold upward and the bladder downward by the means described is as easily accomplished as when one is performing a transperitoneal lower segment operation and prepares two flaps of peritoneum over the lower uterine segment. The lower flap with the bladder is easily pushed off the uterus from above downward, and the upper flap of visceral peritoneum over the uterus is just as easily separated and is pushed upward. (14) If room is deemed insufficient (and this has been but seldom) then (15) pick up the upper flap made by procedure No. 8 (this flap consists of both the transversalis fascia and the anterior sheath of the perivesical fascia)

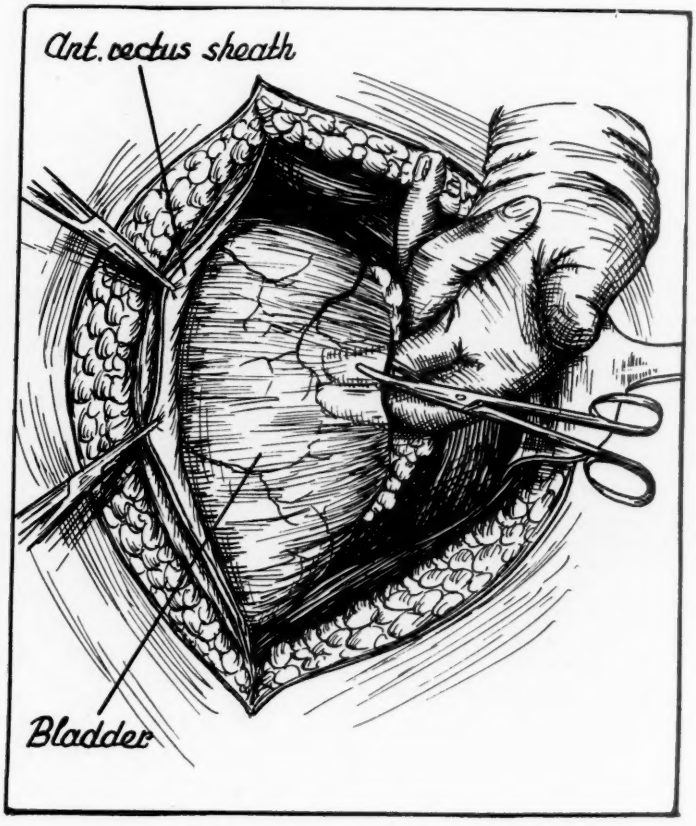

Fig. 2.—The index and middle fingers are insinuated into the left paravesical space in region of chicken yellow fat tissue and the fascia is lifted off the underlying bladder. The direction of the incision of the fascia should be more downward than here represented to avoid injury to anterior peritoneal fold at top of bladder.

which contains within its two folds the anterior peritoneal fold. (16) By traction upward on this flap, and countertraction downward on the bladder, the fascia connecting the anterior peritoneal fold above to the bladder below will be made taut, and the bladder still further separated by incising this taut fascia for any desired distance. The left impervious hypogastric artery may be encountered in effecting this extension across the superior surface of the bladder. Clamp and cut it. (17) The lateral and downward displacement of the bladder should be sufficient to place a vertical incision in the uterus practically in its midline. (18) Inspect peritoneal fold for any evidence of injury; if any is found, repair it. (19) Richardson retractors to hold (1) the peritoneum retracted above and (2) the bladder below

are put in place and vertical incision made in the lower uterine segment or lateral retraction may be made and a transverse incision made in the uterus. (20) Protect the lower angle of vertical incision with gauze pad held in place by retractor and make incision in the midline under direct observation. Thus, no injury can be caused to ureter or any large vessels at the sides of uterus. If vertical incision is used, incise upward from the bladder. (21) Culture taken from open uterus. (22) Deliver infant. (23) Ergotrate given intravenously. (24) Apply "T" clamps to the edges of the uterine incision. (25) Placenta removed. (26) Uterus closed with running No. 2 chromic suture on round Mayo needle. (27) Uterine incision inverted with continuous Lembert suture, using chromic No. 2 on a round Mayo needle. (28) Refill bladder to test for integrity. (29) Place five grams of sulfanilamide in the wound behind bladder. (30) Cigarette drain placed in lower angle of retrovesical space. (31) Approximate the muscle with No. 00 plain catgut interrupted. (32) Close the fascia with No. 2 chromic continuous using cutting edge needle. (33) Close subcutaneous tissue with interrupted No. 00 plain. (34) Dermal Stewart stitch for skin. (35) Remove retention catheter. (36) Drain removed in 72 hours.

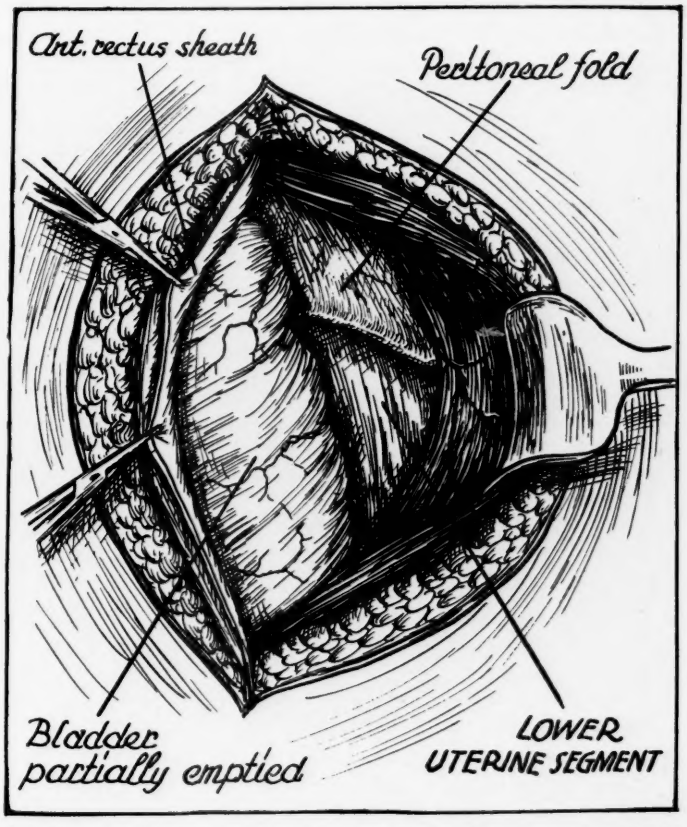

Fig. 3.—Bladder partially removed from lower uterine segment, showing bared triangular space. The upper border is the posterior peritoneal fold; mesial border, the partially emptied bladder; the lateral border, the parieties.

The drawing delineates the infraperitoneal nature of the rest of the operation, viz., remaining below the intact peritoneal fold.

Morbidity Rate and Complications

The average duration of labor for the entire group was 42.6 hours, and the average duration of labor with membranes ruptured was 29.8 hours. The intrapartum morbidity rate was 6.7 per cent. The peritoneal cavity was opened 44 times or in 27.5 per cent of the total. In the earlier cases included in this series, some few patients had the peritoneal cavity opened

deliberately in order to gain more operative room. Nine, or 5 per cent of the total, had the bladder injured, 8 of these occurred in the first 63 cases.

The postoperative morbidity in the entire group was 98, or 61.2 per cent. The standard of morbidity used was a rise in rectal temperature to 100.4° F. on any two readings following the first 24 hours, temperatures being taken every four hours.

There were 9, or 5.6 per cent, stillbirths or neonatal deaths. Thirty-nine, or 24.4 per cent, of the babies born weighed 3,800 grams or more.

There were three maternal deaths. One died in 1935 from infection, and another in 1936 from infection. There was one death in 1938 from hemorrhage.

Report of Fatalities

CASE 1 (History No. 21163).—A 23-year-old, white primigravida, a clinic patient, was admitted to the hospital on Jan. 24, 1935, and had her antepartum course complicated by a right pyelitis. After a labor of 82½ hours, with ruptured membranes for 34 hours, under spinal anesthesia supplemented by ether she had a paravesical cesarean section (Latzko) on Jan. 25, 1935. During the course of the operation the left ureter was severed and the bladder injured. A living 3,640 gram child was delivered. The patient had a septic postoperative course, with a clinical picture of general septicemia, rather than peritonitis, and died eleven days after the operation. At autopsy, there was found a large pelvic abscess at the place of operation, with separation of the cervical wound and left ureter. There was thrombophlebitis of uterine plexus and ovarian vein. An embolic (?) peritoneal abscess in the region of the splenic flexure was found. This is the twenty-seventh case in this series.

CASE 2 (History No. 27073).—A 29-year-old white primigravida with intrapartum temperature 103° F. After 55 hours of labor and 60 hours of ruptured membranes, she was delivered on Oct. 23, 1936, under spinal anesthesia, by a paravesical cesarean section (Latzko) of a stillborn 2,940 gram infant. During the course of the operation, the peritoneal cavity was inadvertently opened. She expired after about thirty hours, with a clinical diagnosis of peritonitis. No autopsy. This is the fifty-eighth case in this series.

CASE 3 (History No. 33298).—A 35-year-old white primigravida, whose labor was 104 hours, and no hours with ruptured membranes, was delivered under cyclopropane anesthesia by a paravesical cesarean section (Latzko) of a living 3,990 gram child Jan. 31, 1938. Immediately following the delivery of the placenta, a uterine hemorrhage occurred from an atonic uterus. The blood loss was estimated at 1,000 c.c. Patient expired on the table. No autopsy. The Latzko paravesical approach was used in all three cases.

There were 116 with an intact peritoneal cavity, of these 69, or 59 per cent, had a morbid postoperative course. Compare this with 66 per cent of those morbid with the peritoneal cavity opened.

With the average duration of labor as high as indicated in Table I, 42.6 hours, and with the average duration of labor with ruptured membranes in the whole group of about 29.8 hours, 11, or 6.87 per cent, had intrapartum morbidity. These figures indicate that the operation in our hands has been reserved for two groups of patients: (1) those who are potentially infected; and, (2) those who are frankly infected. No definition is required to cover the frankly infected patient. That is quite obvious. Some explanation or definition might be in order to cover the "potentially infected" patient. We believe that any patient in labor for a period of eight hours or more with ruptured membranes for a similar duration of time is potentially infected in the sense that pathogenic micro-organisms have already gained access to the amniotic sac; the longer and further this type of labor progresses, the more likely is the patient to be

TABLE I. THE INTRAPARTUM MORBIDITY RATE AND ANTEPARTUM COMPLICATIONS

TOTAL 160 CASES: 11 MORBID INTRAPARTUM MORBIDITY RATE OF 6.87 PER CENT	
Antepartum complications* in this series included—	
Early vomiting of pregnancy	1 case
Hematuria	1
Rheumatic heart disease	1
Pilonidal abscess	1
Hydrocephalus	1
Intercurrent eclampsia	1
Pyelitis	1
Adenoma of thyroid	1
Placenta previa	2
Syphilis	3
Attempted or failed forceps	3
Baggings	4
Failed medical inductions	4
Severe pre-eclampsia	5
Mild pre-eclampsia	8
Unclassified toxemia	9

*The antepartum complications listed were in no sense in any case an indication for the operation, the cases of attempted or failed forceps alone excepted.

TABLE II

YEAR	NO. OF CASES	AVERAGE LABOR IN HOURS	AVERAGE LABOR WITH RUPTURED MEMBRANES	PERITONEAL CAVITY OPENED		BLADDER INJURED		POSTOPERATIVE MORBIDITY		STILLBORN OR NEONATAL DEATHS		BABIES OVER 3,800 GRAMS		MATERNAL DEATHS	
				NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1931-1936	63	42	30.5	23	36.5	8	12.69	43	68.25	5	7.9	18	2.8	2	
1937-1940	44	44	30.0	7	15.9	0	0	26	59.03	0	0	8	1.8	1	
1941-1944	53	42	29	14	26.41	1	1.8	29	54.7	4	7.5	13	2.4	0	
Total	160	42.6	29.8	44	27.5	9	5.6	98	61.25	9	5.6	39	24.4	3	1.87

TABLE III. A STUDY OF THE POSTOPERATIVE MORBIDITY WITH THE PERITONEAL CAVITY OPENED

Total number of cases	160	
Peritoneal cavity opened	44	27.5%
Morbid cases in this group	29	65.9%
Morbid for 1-5 days	19	
Morbid for 6-10 days	5	
Morbid for 11-15 days	4	
Morbid for 20 days	1	

frankly infected. We further feel that this type of patient can best be served if she is to be subjected to a cesarean section by avoiding the contamination of the peritoneal cavity, and we accordingly utilize the operation when the patient has passed from the "clean stage" over to that of the "potentially infected" stage. We have considered some patients to be potentially infected even with apparently intact membranes if they have been in labor for many hours, and have had multiple rectal examinations. No explanation is necessary to cover the management of the frankly infected patient admitted to the hospital as such. The operation is not a procedure to be undertaken electively, and has no place in the management of a clean case by cesarean section. A word of caution is

in order about undertaking the operation in any and all frankly infected patients. Two maternal deaths in this study occurred in this type of patient.

The greatest technical difficulty encountered was the removal of the bladder and the freeing of the posterior peritoneal fold in two classes of patients. Multiparas with previous obstetric difficulty and apparently some old pelvic infection, and a few primigravidas also with old pelvic infection had very dense and fibrotic pelvic areolar tissue, and the structures did not separate easily.

Conclusions

Results obtained in 160 paravesical extraperitoneal cesarean sections are discussed, and a new paravesical approach to the retrovesical infraperitoneal area of the lower uterine segment is presented. (1) There were three maternal deaths in the 160 cases (two due to infection, one to hemorrhage); (2) the peritoneal cavity was opened 44 times (27.5 per cent). The bladder was injured 9 times (5.6 per cent) (eight times in the first 53 cases); (3) 98 cases (61.2 per cent) had postoperative morbidity; (4) the inadvertent opening of the peritoneal cavity did not impair the usefulness of the operation; (5) injury to the ureter occurred but once (case No. 27 in this series).

Speaking now specifically and directly of the technique here outlined, it is claimed: (1) relatively easy access is gained to the retrovesical area of the lower uterine segment; (2) identity of the posterior peritoneal fold is thus possible; (3) this retrovesical area can be enlarged under direct vision infraperitoneally; and, (4) sufficient room obtained to deliver baby of more than average size. (5) In the use of this technique there was no injury to any ureter or any large vessel at site of uterus; the ureter was never within the field of operation. There was no extension of incision into broad ligament at either side; no massive infection of pelvic cellular tissue occurred. There were no injuries to bladder in vesicovaginal area; there were no permanent vesicovaginal fistulas; there were no maternal deaths. (6) Adequate exposure for either a vertical or transverse incision in uterus is obtained. (7) The operation is well within the capacity of any competent obstetric surgeon.

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A CASE OF CLOSTRIDIUM WELCHII PUERPERAL INFECTION TREATED WITH PENICILLIN

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IN THE Johns Hopkins Bulletin of 1897, Dobbin published the first report of puerperal infection due to *Clostridium welchii.* Many cases have been described since, so that when Hill[1] wrote, in 1936, 84 cases were on record, to which he added 30, with a 63 per cent mortality in his own group. Sadusk and Manahan,[2] in reviewing the literature in 1939, found a mortality of 85 per cent for patients not treated with specific antiserum, and 47 per cent when treated with it. Infections with the gas bacillus may follow the birth of a viable fetus or may follow a spontaneous or, more commonly, a criminal abortion. Sixty to 75 per cent of puerperal *Cl. welchii* infections are said to be post abortal.

Clostridium welchii, more commonly known as the "Gas Bacillus," is a short, thick, spore-forming, nonmotile rod which grows under fairly strict anaerobic conditions. The bacillus is found in soil, milk, water, dust, sewage, decaying animal and vegetable matter, and in the intestinal tract of man and animals, as well as a normal or pathogenic inhabitant of the human vagina.[3, 4] "Stormy fermentation" of milk is its most characteristic cultural attribute with the formation of clot, acid, and gas. Two types of exotoxins may be elaborated a hemotoxin and a myotoxin, the pathogenicity of a particular strain depending upon their elaboration. The organism is highly invasive.

Pathologically, puerperal gas gangrene may vary from a very mild infection, limited to the superficial layers of the endometrium and decidua and any retained products of conception, to a very severe infection involving the whole uterine musculature. From this, it spreads by direct extension or through the lymphatic channels to the peritoneum; invading the blood stream, it may metastasize to all the muscles of the body. The milder cases carry a good prognosis, but the more severe ones are associated with an extremely high death rate.

A typical, severe, Welch bacillus postabortal infection presents a characteristic picture: A patient who is acutely ill, yet mentally alert. She runs a low-grade temperature, associated with a tachycardia out of proportion to the fever. There soon develops a striking, and when once seen, a never-to-be-forgotten, icterocyanosis. Signs of marked hemolysis with hemoglobinemia, hemoglobinuria, and anemia rapidly become evident. Milder cases may display only jaundice, without the serologic or urinary evidence of blood destruction. Still others display symptoms far removed from the original focus of infection in the genital tract; these are pain in the deep skeletal muscles, and an overwhelming toxemia. This syndrome is due to the myotoxin of the *Cl. welchii,* and death follows within a few hours of its onset.

The infection which follows the delivery of a viable fetus is more difficult to diagnose, but, in the main, more closely resembles cases of metastatic gas gangrene, than those in whom the hemolysis is the predominating symptom. However, the clinical picture may be so masked that the diagnosis is initially or entirely bacteriologic. More typically, pallor, tachycardia, peripheral cir-

culatory failure, sudden onset of severe uterine pain, with or without jaundice, are the symptoms leading to the suspicion of such a gas bacillus infection.

The importance of the early diagnosis of severe gas bacillus infections with their rapidly fatal outcome in most untreated cases is quite obvious.

There is much discussion in the literature about the necessity of surgical intervention, either by curettage or by complete excision of the infected uterus.[5] Hill[1] and some others recommend the early, careful curettage of the uterus if the infection does not seem to have spread beyond the superficial layers of the decidua. If physometra, either alone, or with peritonitis, exists, then immediate total hysterectomy is indicated, according to them. It must be borne in mind that this advice was given before the sulfonamides or penicillin came into clinical use.

Once the diagnosis has been established, supportive and specific therapy must be begun without delay. General, supportive treatment consists of forcing fluids, both orally and parenterally, in anticipation of oliguria or complete anuria; repeated whole blood transfusions; administration of alkalis to combat the acidosis created by the organism, and to raise the pH of the blood in order to make the bacterial toxins less stable, and further, to alkalinize the urine in order to prevent precipitation of acid hematin in an acid urine. Finally, an attempt must be made to combat a renal shutdown, if it should occur. General treatment as outlined is important but, without the use of more specific therapy, only a 15 per cent cure is realized. The value of the *Cl. welchii* antitoxin is undoubted; it is administered intravenously and intramuscularly. It should be stressed that delay in initiating its use, inadequate dosage, and too early cessation of the anti-serum is almost tantamount to not giving it at all.

After the introduction of the sulfonamides in 1937, Bohlman[6] and Kennedy[7] individually reported the successful use of sulfanilamide in the treatment of surgical infections due to the Welch bacillus. Sadusk and Manahan,[2] noting the experience of these workers and others, were the first to report dramatic results in the treatment with sulfanilamide of puerperal infection caused by this organism. Hunt,[8] in a review of the literature of chemotherapy in obstetrics and gynecology during the five years prior to 1944, concluded that the sulfonamides were of definite value in the treatment of infections of the parturient genital tract caused by the *Cl. welchii,* but pointed out that they must be given early, in large dosage, concomitantly with their specific antiserum.

A new and much more promising chemotherapeutic agent for *Cl. welchii* has recently been added to our drug armamentarium, namely, penicillin. Experimental work by Hac and Hubert,[9] and McIntosh and Selbie,[10] has shown the effectiveness of penicillin in the treatment of experimentally induced *Cl. welchii* infections. Penicillin was shown to be much more effective than other agents such as proflavine, the sulfonamides, tyrothricin, zinc peroxide, zinc oxide, and hyperol (hydrogen peroxide and urea). Efficiency varied directly with the time interval which elapsed from the onset of the infection to the onset of therapy. A therapeutic dose of penicillin given subcutaneously to mice at the time of intramuscular inoculation with the gas bacillus protected 98 of 100 mice so infected.

Since this experimental work, penicillin has been successfully used in the treatment of clinical cases of gas gangrene. There are not many reports in the literature of penicillin therapy of gas bacillus infections, but all relate dramatic results following its use. McKnight, Lowenberg, and Wright[11] were apparently the first to report a human case. Gas bacillus infection set in following a compound fracture of an arm in a 7-year-old girl. All routine

therapy was used, specific antitoxin, sulfanilamide, and amputation with little improvement, while awaiting the arrival of penicillin by plane. Dramatic results followed the intravenous administration of penicillin. McAuley and Gearhart[12] reported the successful use of a continuous intravenous drip of penicillin for twelve days with a total dosage of 1,580,000 units, after the unsuccessful use of sulfadiazine. This was in a case of gas gangrene following a simple, comminuted fracture of the femur. Pickett[13] reports an accident occurring to two soldiers: one suffered a compound comminuted fracture of the surgical neck of the humerus with extensive laceration of the arm and shoulder; the other, extensive lacerations of the calf contaminated by debris and dirt. Both were treated surgically plus the use of plasma and blood transfusions in conjunction with sulfonamide therapy, both orally and locally. Despite these measures, both patients developed severe gas bacillus infections which finally responded to penicillin. Total penicillin dosage in the former case was 6,680,000 units and in the latter, 1,525,000 units.

Kepl, Ochsner, and Dixon[14] report the treatment of two cases of gas gangrene. In the first, gas bacillus infection followed a shotgun injury with the development of cellulitis which was treated successfully by the local application of calcium penicillin over a period of six days. In the other case, the infection followed lacerations of the arm by broken glass and was treated by guillotine amputation combined with systemic and local penicillin. These observers issue a word of caution, stating that penicillin is of most value when combined with timely surgical intervention.

A search of the literature reveals no further clinical reports on the use of penicillin in gas gangrene infections. It should be noted that all the cases were traumatic accidents with secondary invasion by the *Cl. welchii*. To our best knowledge, no case of postpartum or postabortal gas gangrene treated by penicillin has yet been reported, and it is the purpose of this paper to report the treatment of a patient who developed a severe gas bacillus infection following a spontaneous six-month abortion.

Case Report

L. M., a 30-year-old, married, white, graduate nurse entered the hospital on March 5, 1945, because of premature rupture of the membranes and a pregnancy of six months' duration. She was not in labor. Her last menstrual period had begun October 4, 1944.

Ten years ago, while a student nurse, she had had an amputation of the cervix because of its hypertrophy with protrusion of the external os through the vaginal orifice. In June, 1944, her first pregnancy ended in the spontaneous expulsion of a four and one-half-month fetus following a very sudden and profuse gush of blood. Her present pregnancy was similarly complicated by a sudden gush of blood six weeks before admission. The patient remained in bed for six weeks and was then allowed up. Two days later, her membranes ruptured and she was hospitalized in the maternity.

In the hospital, she leaked amniotic fluid for four days without the onset of labor. She was then transferred to the delivery room and her cervix exposed with a bivalve speculum under aseptic precautions. It was found to be closed. The patient was then returned to her own room. Two days later, she went into labor and after one to two hours, delivered herself in bed of a stillborn, unmacerated fetus, 30 cm. in length. The placenta was easily expressed with a blood loss of less than 50 c.c. The abortion occurred at 10:45 A.M. on March 10, 1945. At 8:00 A.M. on the same day, the temperature was elevated for the first time; it was 101° F. by mouth.

The following morning, March 11, 1945, she complained of headache, sweating, pains in the back and abdomen, and marked weakness. Her skin was deep bronze, her lips and fingernails cyanotic. The sclerae were yellow, and she passed port wine colored urine. The temperature and pulse were normal and the blood pressure was 120/80. The white blood count was 52,000, with 93 per cent polymorphonuclear cells. Blood serum drawn for

determination of the icteric index was red. Hemoglobin and red blood count which had been 60 per cent and 3.5 million, respectively, on admission, were now 54 per cent and 2.21 million. The urine was negative for bile but positive in a 1 to 400 dilution for urobilin. Intrauterine culture taken at 8:00 P.M. on March 11, 1945, was reported positive 12 hours later for *Cl. welchii*. The urea was 92 mg. per cent (normal range 25 to 40 mg. per cent). The patient seemed to be very ill. A blood culture taken at the time of the uterine culture* remained negative throughout.

It was recognized that we were probably dealing with a case of Welch bacillus puerperal infection and, without waiting for the report from the uterine culture, 40,000 units of penicillin were given intramuscularly at 9:00 P.M. on March 11, and 20,000 units every three hours intramuscularly, from then until a total of 1,200,000 units had been given. Five hundred cubic centimeters of citrated whole blood were given on March 11 and repeated on March 12, March 13, March 15, and March 19.

Jaundice decreased promptly, and the patient felt better the day after penicillin was started. Actual recovery, however, was prolonged. The blood urea continued to rise in spite of the adequate output of dilute urine, reaching a peak of 191 mg. per cent on the eleventh day and returning to normal twenty days later. On the seventh day, the blood pressure rose to 185/100, remained elevated for seven days, then returned to normal. The white blood count returned to normal, and the hemoglobin and red blood count after the five transfusions rose to 96 per cent and 4.5 million, respectively. The temperature and pulse, with exception of one rise on the fifth day, remained approximately normal. On the fifteenth day, the patient developed twitchings of the extremities that persisted in spite of sodium lactate and calcium gluconate intravenously. These twitchings continued intermittently for approximately two weeks. On March 21, 1945, the twelfth postabortal day, the phenolsulfonphthalein test revealed a total output of 25 per cent of the dye in two hours. On the sixteenth day, six days after penicillin was stopped, the temperature rose to 103° F., the patient had a sharp chill, and a catheterized specimen of urine was loaded with pus cells. A full-blown, colon bacillus pyelonephritis developed. This subsided in five days, during which 140,000 units of penicillin, and 10 grams of sulfasuxidine daily, were given. The other sulfonamides were thought to be contraindicated because of the elevated blood urea.

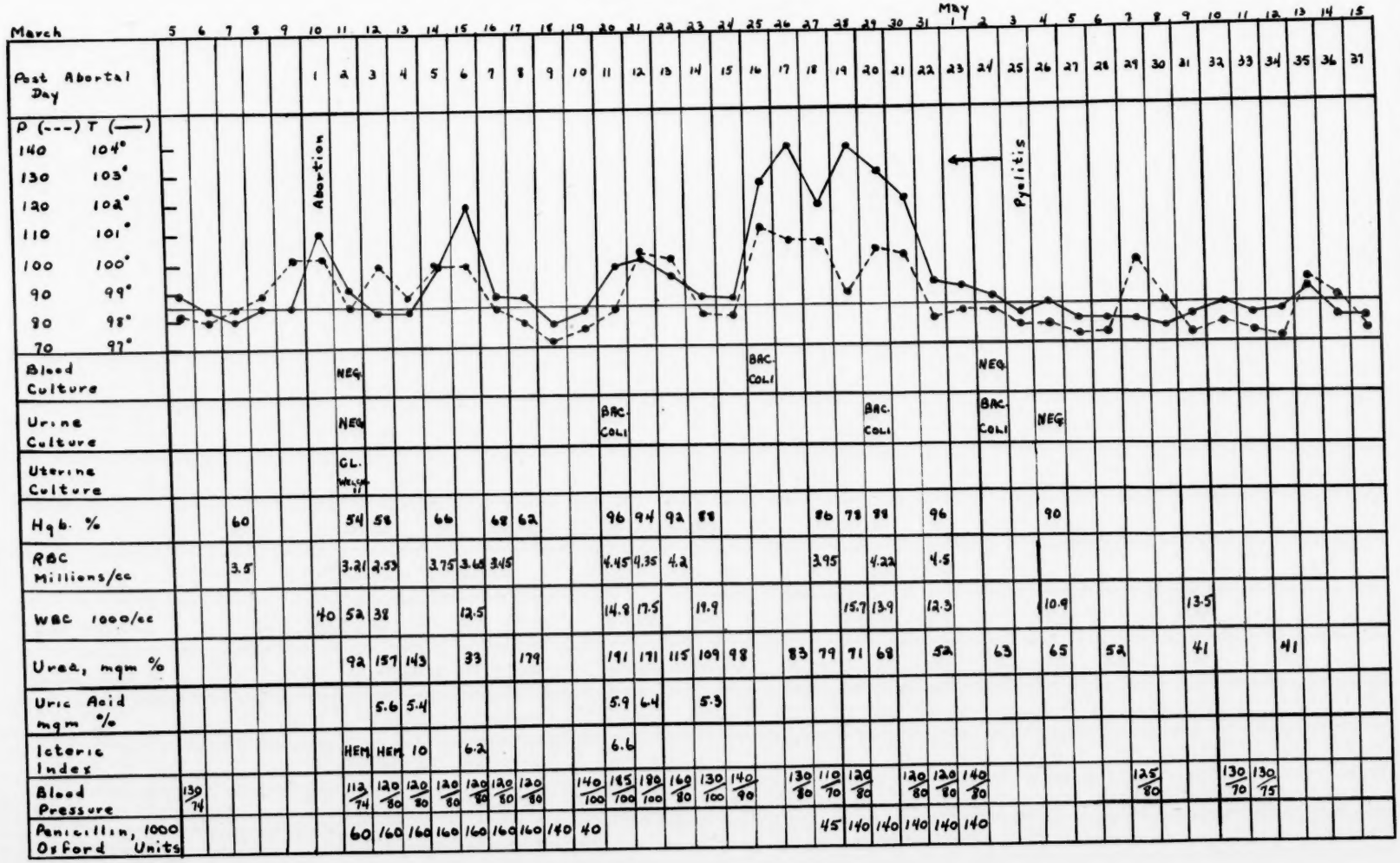
The patient left the hospital on April 15, 1945, thirty-seven days after onset of the *Cl. welchii* infection, with a normal blood pressure and urea. Her phenolsulfonphthalein test had risen to 60 per cent excretion in two hours, and the patient was able to concentrate her urine to a specific gravity of 1,015. See Figure 1 for clinical and bacteriologic studies.

Discussion

The case history presents a picture of a moderately severe, postabortal infection due to the gas bacillus. The probable etiological factor was the presence of ruptured membranes for five days before abortion occurred. There is no history of criminal intervention and, indeed, this can be completely ruled out from the history. The pulse and temperature were normal until the day of the abortion and remained essentially normal through the height of the infection. Signs and symptoms, however, were quick to assert themselves after the abortion, so that within 24 hours, the patient was markedly jaundiced, superimposed on which was a cyanotic hue, especially evident in the lips and nailbeds. The patient looked ill and became toxic and lethargic. Penicillin therapy was begun some thirty-four hours post abortion and 12 hours after the patient became so ill. In six hours after the initiation of penicillin therapy, the patient was clinically improved, and her overwhelming toxicity had almost completely disappeared.

*Through a misunderstanding in the laboratory, the original blood culture was not planted anaerobically for 12 hours after the blood was drawn. At this time, 1 c.c. of the diluted aerobic broth culture was then planted anaerobically.

FIGURE 1


March
May
Post Abortal Day
P (---) T (——)
140 104°
130 103°
120 102°
110 101°
100 100°
90 99°
80 98°
70 97°
Abortion
Pyelitis
Blood Culture
Urine Culture
Uterine Culture
Hgb. %
RBC Millions/cc
WBC 1000/cc
Urea, mgm %
Uric Acid mgm %
Icteric Index
Blood Pressure
Penicillin, 1000 Osford Units
NEG.
BAC. COLI
CL. WELCHII
HEM.

Other typical clinical features were: (1) the high white blood count with the marked shift to the left, (2) port wine urine, (3) the sharp drop in hemoglobin and red count, (4) hemoglobinemia, (5) positive uterine culture of *Cl. welchii.* A subculture was made and ½ c.c. was injected intramuscularly into a 285-gram guinea pig. The guinea pig died twenty hours after the inoculation and at autopsy showed: (a) serosanguineous gaseous exudate at the site of injection, (b) peritonitis with the same kind of fluid, (c) cultures of the fluid from the site of injection and in the peritoneal cavity showed pure *Cl. welchii,* (d) the vena cava and inguinal veins showed gas bubbles.

As previously stated, the response of the *Cl. welchii* infection to penicillin therapy was prompt and dramatic. The marked anemia was successfully combatted with frequent whole blood transfusions. Uremia, apparently due to massive blood destruction by the bacterial hemolysins, was quite persistent despite the forcing of the oral and parenteral fluids and in the face of an adequate urinary output. The pathology underlying the later development of hypertension and tetany are still unclear, but apparently responded to intensive calcium gluconate, intravenous fluid, and alkali therapy.

The question arises whether the result obtained might not have been even more satisfactory had a specific antiserum been used in conjunction with the penicillin, the latter to combat the organism itself, and the former to neutralize the toxins which had already been produced before the initiation of therapy.

Conclusions

A case of moderately severe postabortal puerperal infection with *Cl. welchii* was successfully treated with penicillin given intramuscularly in a total dosage of 1,200,000 units. The patient's condition improved within six hours after commencing therapy. The possibility that combined penicillin and specific antitoxin therapy may be more rational and potentially more effective is suggested.

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VAGINAL HYSTERECTOMY

A Record of Results Based on the Weir Technique

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THE increasing popularity within the last few years of vaginal hysterectomy, like total abdominal hysterectomy, is evidenced by the large number of publications appearing in the current medical journals. In spite of the usefulness or advantages of this operation, an occasional article will appear, not only overlooking the merits of vaginal hysterectomy, but condemning it.[1] In reviewing the history of this operation, one has to agree with Cogswell[2] that it has weathered transient periods of popularity and unpopularity.

Knowing that any so-called routine technique must be modified in each individual case, the description of a number of techniques and the end-results statistically by various operators or clinics obviously proves to be of inestimable value in evaluating the operation and adds to its refinement. Thus a description of our method and the end-results seem justified. However, we would not want to convey the idea that every case of uterine prolapse with cystocele, rectocele, and other accompanying lesions, such as urethrocele or enterocele, can be corrected by one type of hysterectomy. As Masson[3] states, the treatment must embrace the same surgical principles employed in the correction of any hernia as found elsewhere in the body.

In reviewing our records from 1928 to 1942, there were 6,017 hysterectomies done. From this total, 3,641 were abdominal hysterectomies and 2,091 were supracervical hysterectomies. Three hundred and eighty-five vaginal hysterectomies were done, or a percentage of 6.39.

The history of vaginal hysterectomy is of marked interest and has been adequately covered in many excellent articles and monographs.[4, 5] As stated by Emmert,[6] most of the reports in the literature fall short of giving the percentage of failures, the undesirable sequelae which are bound to occur in some cases, regardless of who performed the operation.

The method employed on the Gynecological Service of University Hospitals varies with the individual operator. However, the ward service handled by the Resident Staff follows the technique of Dr. W. H. Weir. It is for this reason that only Dr. Weir's cases and those of the staff ward service with a similar routine technique have been reviewed. The number of cases embraced in this report is 205, of which 88 are private cases of Dr. Weir* and 117 are ward cases.

*The authors have had, through the kindness of Dr. W. H. Weir, complete access to his private records, and desire to thank him for his helpful criticism.

In reviewing the histories, the frequency of postoperative cystitis is, of course, striking. This condition, which practically always cleared up before the patient went home, is no doubt due to several factors such as: (1) the large number of cystoceles present at operation with residual urine, (2) postoperative catheterization or constant drainage, (3) the inevitable operative trauma to the bladder in dissecting it free from the uterus. Further, there were more unsuccessful or unsatisfactory results on the ward service than on the private. This is perhaps due in some degree to lack of skill, although there is strict supervision by the Chief Resident or a Departmental Head.

Description of Operative Technique

The cervix is first transfixed with a heavy silk or linen suture for making traction. This will not tear out and it is generally more satisfactory than any tenaculum forceps. The cervix is pulled as far down as possible, and a transverse semicircular incision made through the mucosa at the vagino-cervical junction. A short incision is made upward from this one in the midline and the two angles of mucosa are separated by sharp dissection from the underlying tissues around and on either side as far as the lateral fornix. A pair of blunt scissors can now be easily worked up under the vaginal mucosa to just below the urethra and the mucosa is then incised in the midline up to this level. The triangular flap of mucosa on either side can then be easily stripped off from the surface of the bladder far over on either side. The bladder is then dissected free from the anterior uterine surface and completely separated at the sides as well, so that it can be pushed up freely under the arch of the pubes, exposing the whole anterior uterine surface. The vesico-uterine peritoneal reflection is then opened from side to side, or this may be done later, after the lower pedicles have been tied and divided when the finger may be passed up behind the uterus and over the fundus. The exact relation to this peritoneal fold is then easily determined.

Traction is then made upward on the cervix, and the mucosa of the posterior fornix incised from side to side and Douglas' pouch opened. With a finger in this pouch and the thumb anterior to the broad ligament, the attachment of these lateral supports is easily identified. They are ligated with a double strand of chromic gut and divided close to the cervix, well inside the ligature. As soon as this pedicle is divided, the uterus comes down much more readily with traction. The tissues on the other side are ligated and divided in the same way. If the uterus comes well down, the remaining attachments on each side (the round ligament, tube, ovarian ligament, and ovarian artery) are ligated with a double strand of chromic gut and divided well inside the ligature. A clamp is placed on the pedicle to prevent its retraction, and the ends of the ligature cut so that no traction will be made on it, for fear of pulling it off. If the uterus is large or does not come down readily before ligating this pedicle, the fundus may be delivered posteriorly which will facilitate passing the ligature and tying the pedicle. A similar pedicle is ligated on the other side and the tissues divided, completing the separation of the uterus. If the tube and ovary are to be removed, the infundibulopelvic ligament is tied outside the tube and ovary, the tissues divided well inside the ligature, and the stump allowed to retract. In this case, the round ligament alone would represent the pedicle on this side. It would be ligated and divided close to the cornu. The two upper pedicles are then stitched together with a double No. 2 catgut, and this stitch includes the peritoneal edge of the vesical reflection. If the pedicles are very lax, they may be overlapped. The prolapsed bladder is now pushed up above these sutured pedicles and the base of the bladder, at a point just above the trigone, is sutured to these united pedicles with a single ligature. The cystocele will then be held up at the proper level, but is further supported by later suturing the pubovesical fascia from either side in the midline.

The two lower pedicles are then sutured together with a double strand of chromic catgut, which also includes the peritoneal edge of the cul-de-sac, first dissecting out and

excising the sac of any existing enterocele. The ligatures uniting the two upper and the two lower pedicles may be tied together approximating all the supports in a single sling, but in the rare cases in which drainage is used, a cigarette drain is inserted into the cul-de-sac, between the two, and they are not tied together.

The pubovesical fascia, just beneath the mucosa on either side is united in the midline beneath the bladder by several chromic gut sutures from just beneath the urethra down to the former site of the cervix. The excess mucosa is then resected on either side, and the remainder sutured in the midline with a continuous stitch. Repair of the perineum, in the usual way, completes the operation.

Advantages and Disadvantages

There are some inescapable advantages for vaginal hysterectomy such as:

1. The total operation, viz., the hysterectomy, repair of the anterior vaginal wall, correction of cystocele, excision of enterocele if present, perineorrhaphy can be done at the same time.

2. Patient is not subjected to such a long operation as when the abdominal procedure is done.

3. It is a total hysterectomy, thereby removing the cervix and relieving the patient of a chance for subsequent development of carcinoma of the stump. Further, according to J. Hamilton,[7] when subtotal hysterectomy is done the chances for a prolapse are greater than with a total hysterectomy.

4. Morbidity is less.

5. Operation may be carried out with general, local, perineal pudendal block, or spinal anesthesia.

6. Patient may be up sooner.

7. Pulmonary complications are less frequent.

8. Operative time is shorter.

There are certain disadvantages not to be overlooked, and certain conditions make the operation more difficult, such as:

1. Large tumor (myoma) of the uterus offers difficulty. In these cases, we prefer the abdominal route, although many men choose morcellation and piecemeal extraction per vaginam.

2. Small vaginal outlet which interferes with good exposure makes ligation of vessels and reconstruction of the pelvic sling difficult. The operation is often longer and more traumatic to the patient than the abdominal. The clamp method or a Schuchardt paravaginal incision will often obviate this condition. However, we do not use the clamp method at the University Hospitals.

3. Adherent or fixed uterus due to pelvic adhesions, endometriosis, and those adnexal lesions too difficult to remove by the vaginal route.

4. Rarely, but occasionally, previous suspension may render the operative procedure difficult.

Since it is not an infrequent observation to find cystocele, rectocele, prolapse uteri, and even procidentia, in nulliparous women, the finding of a slight degree of prolapse after vaginal operation should not be too severely criticized. The failure to correct an enterocele, urethrocele, etc., at time of operation is simple negligence, and unnecessarily subjects the patient to another operation. Two cases of enterocele on the ward service were overlooked at the time of operation.

Postoperative Care

A moist iodoform gauze pack is placed into the vagina for 36 hours and a straight male catheter in the bladder. Both are removed at the same time. Prostigmine (1:4,000) ampules is given every four hours for two to three days with rectal tube. This increases prothrombin time and relieves postoperative distension, and facilitates emptying the bladder. Supportive measures, such as hyperventilation, blood transfusion, etc., are given when

indicated. Morphine, demerol, or dilaudid are given for pain during first three or four days, and later, codeine. Barbiturates are not given freely to elderly patients. Ample fluids are encouraged, usually from 2,500 to 3,000 c.c. daily. Movement of extremities is encouraged. Patients sit up on the seventh day, are out of bed on the eighth, and home on the twelfth.

Discussion

In reviewing the vaginal hysterectomies, we have reported only 207 cases from ward service and those of Dr. W. H. Weir. The technique as described, we feel, has given very satisfactory results. In using the suture method, adequate room (outlet) with good exposure is necessary. We believe that suturing the base of the bladder to the united upper pedicle is an important feature of this technique. Plication of the uterosacral ligaments is extremely important to prevent recurrent prolapse and enterocele. This step is overlooked by many operators.

Two postoperative deaths occurred, one due to pulmonary infarct (ward case) and one to cardio-vascular-renal disease, for which the operative risk was poor and the patient died six weeks after operation.

Scrutinizing the three enteroceles: two were overlooked or not diagnosed at time of operation; one was recurrent and hence must be charged up to an incomplete or inadequate operation. The two cases overlooked were subsequently operated upon and, although subjecting the patient to a second operation, the end-results were successful. There was one very small vesicovaginal fistula which healed spontaneously four months after operation.

Postoperative pelvic abscesses only prolong the hospital stay of a patient. Fortunately this occurred in only one case. We believe that pelvic infections or abscesses are rare because of careful preoperative vaginal toilet. We cleanse the perineum and vaginal vault with tincture of green soap, followed by painting with iodine and 70 per cent alcohol after draping. Also, with traction sutures, the cervix is practically closed. Postoperative hemorrhage is not an infrequent occurrence according to Danforth.[8] There was but one in this series requiring a secondary operation.

TABLE I. RESULTS

Total vaginal hysterectomies—1928 to 1942		385
A review of private and staff patients from the Gynecological Service		205
Unfollowed		7
Follow-up examination from two to ten years		192
Mortality	2	1.04%
Recurrent rectocele	5	2.60%
Recurrent cystocele	7	3.64%
Prolapse of vaginal vault	4	2.08%
Pelvic abscess	1	.52%
Shortened vagina	4	2.08%
Urethrocele	2	1.04%
Stress incontinence	4	2.08%
Enterocele:		
a. Overlooked at time of operation	2	1.04%
b. Recurrent	1	.52%
Vesicovaginal fistula	1	.52%
	17	17.17%
Corrected		
1. Two overlooked enteroceles—later operation satisfactory		
2. Vesicovaginal fistula healed spontaneously, making 14 unsatisfactory cases or		7.07%

Conclusions

1. That vaginal hysterectomy is a procedure of inestimable value is hardly debatable.

2. A review of vaginal hysterectomies at University Hospitals of Cleveland has been presented with the follow-up end results.

3. A description of the method employed by Dr. W. H. Weir has been given in detail.

4. Only the patients of Dr. Weir (private), and the ward employing a like routine technique, have been used.

5. In performing any operation, the operator should utilize the procedure best suited to the individual patient.

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THE MEASUREMENT OF THE DIAMETERS OF THE PELVIC OUTLET*

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IT IS a matter of general agreement among those doing obstetrics that a knowledge of the pelvic diameters of the *inlet* is a sine qua non for the scientific conduct of a case of labor, and yet very frequently the outlet measurements are honored in the breech.

It is the purpose of this paper to urge first, that the study of the outlet diameters be not neglected, and second, to describe a manual method for their estimation, much simpler than any heretofore described. While the importance of the outlet measurements is not as great as those of the inlet, since the incidence of contraction at the outlet is not as frequent as at the inlet; nevertheless, if all the disasters which have resulted from ignorance of the outlet diameters could be tabulated, their importance would be emphasized in no uncertain terms.

There is no question that contractions at the inlet have presented a much more simple problem than do those at the pelvic outlet, since the inlet diameters can be sufficiently accurately measured manually or by x-ray, while on the other hand the outlet diameters have in the past been found to be much more difficult to estimate. This is unfortunate, since grave damage to the mother and baby may well be the result of ignorance of the outlet measurements. While the x-ray measurements are of great value, it goes without saying that many women cannot have the benefit of such a study because of the expense involved or because of the lack of a roentgenologist capable of making the measurements.

It is clear that, if a mistake occurs in pelvic brim measurements, there is always time to perform a cesarean section before the labor has advanced to the point of exhaustion of the mother and damage to the baby. If, however, the outlet is the area of contraction, as is the case in funnel pelves, dystocia may often not be evident until the labor is of many hours' duration, too late for section and too late except for a difficult forceps, or even a destructive fetal operation. Every obstetrician of experience will remember cases in which the early labor progressed in a normal manner but, when the passage of the head through the outlet was attempted, progress ceased and a difficult extraction was necessary, to say nothing of the frequently severe injuries to the soft parts of the mother. It is our belief that in many cases of marked outlet contraction, a cesarean operation should be done before labor, since if it is justifiable to open an abdomen for many conditions not immediately threatening life, an everyday

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occurrence, it is certainly justifiable to do a cesarean section to save the life of a baby and/or to avoid damage to the pelvic structures of the mother, often difficult to repair and in any event requiring subsequent operation.

The senior author's interest in the contractions of the pelvic outlet dates back over forty years to a case reported at the time in the late lamented University Medical Magazine.[1]

> This patient, a doctor's wife, had an ample pelvic inlet, and the labor was rapid and easy until the outlet was reached. Here for a while there was delay with marked elongation of the perineum comparable to the lengthening seen in persistent occiput in the hollow of the sacrum. Then a small round hole opened well back of the fourchette near the anus. In this case, the outlet transverse diameter was so short, or, in other words, the area of the anterior triangle was so diminished that the head was forced to be born through the posterior triangle.

Ever since this experience, which took place before Whitridge Williams' work on the pelvic outlet, we have been impressed with the great importance of the measurements of the pelvic outlet, and have made the outlet transverse estimation an integral part of prenatal examination. However, this one measurement, while it gives information of great value, is by no means all that should be obtained, as will be seen in a moment.

Breisky[2] (1870) was one of the first to emphasize the importance of the outlet measurements, and he invented a special instrument for the measurement of the transverse diameter. But his measurement of the pelvic outlet consisted of only two diameters, namely, the anteroposterior or sacro-pubic diameter between the lower edge of the symphysis and the sacro-coccygeal joint, and second, the transverse diameter between the inner surfaces of the tubera ischii.

Now it must be remembered that, while the pelvic outlet is formed by two triangles, the anterior and the posterior, having a common base which is the just mentioned transverse diameter, the two triangles are not in the same plane, being joined at their common base at an obtuse angle.

Champneys, as long ago as 1884, stated that neither the intertuberous diameter nor the anteroposterior diameter is an accurate criterion of the possibility of delivery. The measurement really needed, but which he said cannot be obtained with accuracy, is the space between a line joining the tubera ischii and the tip of the sacrum. This measurement suggested by Champneys is nothing else than the altitude of the posterior triangle which is now known as the posterior sagittal diameter, and which we believe can be easily determined by our method to be described.

The measurements of the outlet of the pelvis which should be taken routinely are: *first,* the transverse diameter between the inner surfaces of the tubera ischii; *second,* the anterior sagittal diameter, i.e., the distance between the middle of the transverse diameter and the symphysis: *third,* the posterior sagittal diameter, i.e., the distance between the sacro-coccygeal joint and the middle of the transverse diameter; and *fourth,* the pubic angle formed by the junction of the rami of the pubis.

In order to determine the transverse diameter, the senior author invented, many years ago, a very simple little instrument which is portrayed in the last edition of the textbook on obstetrics of the late Dr. B. C. Hirst.

By inserting this instrument between the tuberosities, the examiner is able to obtain an exact measurement, and without the aid of an assistant, which is of great advantage. If the measurement between the tuberosities is 8 cm. or more, the birth prognosis very probably is good as far as the outlet is concerned, but in a nonnegligible percentage of cases of funnel pelvis, this diameter is contracted to such a degree that difficulties are to be expected. If there is too little space in the anterior triangle of the outlet, the posterior triangle must be utilized for the passage of the head. If the posterior triangle is large enough, birth may be satisfactorily completed, though often associated with great damage to the outlet soft parts, but if it is too short, very unfortunate damage to both mother and fetus is not unlikely.

Williams gives a table (Table I) indicating the approximate compensatory increases of the posterior sagittal diameter necessary for various degrees of transverse contraction:

TABLE I

A transverse diameter of	8	cm. demands a posterior sagittal diameter of	7.5
A transverse diameter of	7	cm. demands a posterior sagittal diameter of	8
A transverse diameter of	6.5	cm. demands a posterior sagittal diameter of	8.5
A transverse diameter of	6	cm. demands a posterior sagittal diameter of	9
A transverse diameter of	5.5	cm. demands a posterior sagittal diameter of	10

Ever since the time of Champneys, 1884, obstetricians have been attempting to evolve a method which will allow at least a proximate estimate of the posterior sagittal diameter. Many instruments have been invented as those of Klien, Williams, Thoms, Breisky, and others. They take the measurement of the posterior sagittal externally, deducing a small factor because of the thickness of the sacrum, but the points between which the measurements must be taken are not prominent, and the obtaining of anything more than an approximation of the true measurement is, to say the least, very problematic. Moreover, these instruments cannot be used without the aid of an assistant.

Technique

Our technique for the measurement of the postsagittal diameter is simplicity itself and is as follows: The instrument (Fig. 1) used to measure the length of the transverse diameter of the outlet is placed between the most prominent points on the inner surface of the ischian tuberosities, said points having been marked with ink. This measurement having been obtained, the index finger is passed *into the rectum,* and without difficulty the little depression at the junction of the lower end of the sacrum and the first coccygeal vertebra is located. It is an advantage to have the patient draw her knees up until the anterior surfaces of the femoral regions are in contact with the anterior abdominal wall.

The hand is raised slightly until the rectal finger is bisected by the imaginary line between the ink marks on the tuberosities. The nail of the other hand marks this point, as in taking the diagonal conjugata of the inlet and the pelvimeter gives the number of centimeters.

A modification of the method may be made as follows: The transverse measurement of the outlet between the tuberosities having been taken, the finger is introduced into the rectum and the little dimple which marks the junction of the lower end of the sacrum with the coccyx is palpated, then the instrument for the transverse measurement is again placed in position and the point at which it impinges on the rectal finger is marked by nail pressure, and this distance between said mark and the tip of the finger gives the length of the post-sagittal diameter. This method for the measurement of the posterior sagittal is rendered easy by the fact, as shown by Breisky, that the transverse diameter crosses the upper edge of the anus. Through the vagina this measurement is impossible because of the perineal body, but if the rectal method is used it becomes marvelously easy, and it has given us so much satisfaction that we felt that it should become common knowledge.

Fig. 1.

One paper which we have found since we began our present technique missed our simple procedure by a very small fraction. The author of this paper was Hansen, who, in 1934, published his instrument for measuring the posterior sagittal directly. This instrument consisted of a rod with a ring at the distal end into which he placed the index finger, and then introduced finger and instrument into the rectum, and under guidance of the finger placed the end of the rod upon the junction of the sacrum and coccyx, reading off the number of centimeters on the scale upon the shank of the rod. Why, having gone so far, he did not realize that the rod was unnecessary, is hard to understand. In any event, such is the case, as we have repeatedly demonstrated.

For the complete measurement of the outlet, therefore, not only must the two diameters mentioned above, namely, the transverse and the posterior sagittal, be obtained, but also, as has been said, the anterior sagittal and the subpubic angle. To measure the anterior sagittal, the same method is used as for the postsagittal, namely, a finger in the rectum which easily reaches the junction of the pubic rami, then the imaginary line between the ink-marked tuberosities is noted and a nail mark is made where said line bisects the finger in the rectum, and the number of centimeters is shown by the pelvimeter. Having obtained this measurement, the estimation of the pubic angle, i.e., whether it is 90° or greater, or less than 90° is simplicity itself, since in an isosceles triangle the angle found by the juncture of the two equal sides must be 90° of the altitude, i.e., in this case the anterior sagittal is one-half of the base line, namely, the intertuberous diameter. If the anterior sagittal is less than half the base, the subpubic angle will be more than 90°; while if the length of the anterior sagittal be more than half the base, the subpubic angle will be less than 90°.

The importance of the estimation of the angle formed by the junction of the pubic rami is that if the length of the pubic rami is increased the angle will be lessened, even though the base, i.e., the intertuberous diameter, is ample, hence the head will necessarily impinge more deeply than normal into the posttriangle.

Comment

The measurements just described, namely, the anterior and posterior sagittal diameters, together with the transverse diameter give a very definite picture of the capacity of the outlet, of great value in prognosis of labor and

the choice of treatment. A small amount of practice will enable anyone to make the measurements just described with more accuracy than by the use of the complicated instruments which have been devised for this purpose, and no one of experience will fail to realize the added comfort to the attendant and safety to the patient.

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Discussion

DR. ROBERT TAUBER.—Sometimes it is difficult to find the little dimple over the sacrococcygeal joint when taking the posterior sagittal by inserting the index finger into the rectum. In these cases it is advisable to bring the hips of the patient beyond the edge of the table and to examine bimanually. The coccyx can easily be moved and the joint palpated beyond doubt.

I would like to say also a few words about the measurement of the subpubic angle. The anterior triangle of the outlet is an isosceles triangle. The pubic rami are the equal lines and the angle between the pubic rami is the subpubic angle. The basis of the triangle is the transverse diameter which we can measure between the inner surface of the tuberosities. The altitude of this triangle is the anterior sagittal which forms with the transverse diameter an angle of 90 degrees. This right angle allows us to figure the exact size of the subpubic angle, because, according to the trigonometric rules, the tangent of the half of the subpubic angle is equal to the opposite side (which is the half of the transverse diameter) divided by the adjacent side (the anterior sagittal). Therefore we can obtain the exact size of the subpubic angle by the measurement of the transverse and the anterior sagittal diameter. What we need to know is only whether the angle is 90 degrees or less.

If the anterior sagittal is equal to one-half of the transverse diameter, the subpubic angle is 90 degrees.

If the anterior sagittal is equal to two-thirds of the transverse diameter, the angle is 74 degrees.

These two rules are easy to keep in mind, and the knowledge of the size of the subpubic angle, in addition to the measurement discussed by Dr. Nicholson, permits us to judge whether the outlet is big enough for a normal delivery or not.

DR. A. E. COLCHER.—Drs. Nicholson and Tauber have developed a simple bedside method of estimating the measurements of the anterior and posterior segments of the outlet. Its value lies mainly in the field of markedly frank disproportion. A test of labor is necessary to see whether the presenting part can be brought down to the pelvic floor. If it is not, then the measurement is of no value. If it is, then it is a little late for section and a difficult outlet procedure must be resorted to. If a narrowed outlet is present, one would surmise that the actual inlet and midpelvis would be similarly contracted. One does not section a case because of borderline outlet measurements. Therefore, a method giving the maximum of information is desirable. Such a method was described by Dr. Walter Sussman and myself in the *American Journal of Roentgenology*, February, 1944. This method embodies all diameters, and measurement of the subpubic angle can be read instantly from a prepared chart. We have found that an ample posterior segment of the outlet and an acute subpubic angle offer no obstruction. If the posterior measurement is narrow and the subpubic arch acute, a problem is presented.

DR. NICHOLSON (Closing).—I would first of all call Dr. Colcher's attention to the relative frequency of the funnel pelvis in denying his statement that "if a narrow inlet is present one would surmise that the pelvic inlet would be similarly contracted." This is really the reason for the presentation of this paper.

As stated, we hope that the simple method here given will lead those doing obstetrics to give greater attention to the outlet measurements. Our experience with this method has proven its dependability and but little practice will be necessary to enable anyone to become expert in its use.

It might also be said that a relative contraction at the outlet may be definitely an indication for a cesarean section, but of course the decision should be made very early in labor, long before the head has reached the perineum.

THE PSYCHOSOMATIC TREATMENT OF HYPEREMESIS GRAVIDARUM BY HYPNOSIS

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THE treatment of hyperemesis gravidarum is still a common problem in obstetrics. The numerous methods in use today are prima facie evidence that none have proved exceptionally successful, even though a wide variety of these methods have yielded relief in some patients.

Kosmak[1] states, "the cardinal fact to be borne in mind is that no routine method applicable to all cases can be recommended, but in each instance, particularly in the more severe type, consideration must be given to the individual patient." In other words, treat the patient and not the disease.

It is acknowledged by many investigators that the relief of nausea and vomiting of pregnancy may often be the result of unintended suggestion derived from the therapy, regardless which method is used. Such results are in agreement with the theory held by many that there is a definite psychic factor associated with this condition, and the principal feature is an underlying psychosomatic condition. These factors are responsible, in part at least, for most instances of vomiting during pregnancy. If they are allowed to persist they can cause this type to merge into the toxemic or pathologic type. For thirty years Sir Arthur Hurst[2] has been convinced that the so-called pernicious vomiting is always hysterical in nature. He rejects the theory that a toxic form of the vomiting of pregnancy exists and that the division into nervous and toxemic cases is fallacious. He states that nearly all cases are curable by psychotherapy alone. DeLee and Greenhill[3] state, "A functional disturbance of the nervous system is at the bottom of many cases of hyperemesis. Hyperemesis is amenable to suggestion, and most of the cures we accomplish are due to it." Williams[4] laid great stress on the fact that mental suggestion alone will cure over 50 per cent of all cases.

In studying this group of patients, we have learned that these individuals consciously have one attitude toward the pregnancy, while unconsciously they harbor a totally different one. Because a woman is constituted by nature to bear children, it does not mean she may wish to do so, even though she consciously professes a desire for pregnancy.

W. Menninger[5] states, "One learns from psychiatric experience that many women have no interest or desire to have a child, many others have unconscious aversion to pregnancy but express conscious desires based on illogical, immature, or even irrational consideration. In either case, one may expect that the mother would suffer during pregnancy, and that the conflict would display itself in a total organism reaction, both psychological and physiological."

An important emotional attitude influencing the pregnancy state is the inability to adjust oneself to it, even though conscious acceptance of the pregnancy

is manifested. The vomiting which occurs is but an expression of unconscious rejection of the pregnancy in some women. Another group consists of women who have long desired pregnancy and who believe that nausea and vomiting are a real part of it. When one of these women misses a period she eagerly looks forward to the onset of the "morning sickness" to clinch the proof that she is really pregnant, and when it appears she gives it all the aid in her power.

For a thorough survey on the more important psychological stresses and strains associated with pregnancy and a few of the manifestations of these, the reader is referred to W. Menninger's[6, 7] extensive study on the importance of pregnancy as one of the major experiences in the life of a woman, both psychologically and physiologically.

K. A. Menninger[8] has outlined many other somatic manifestations by which a woman may indicate her unconscious repudiation of her femininity. Because hyperemesis gravidarum is common, every obstetrician should have a thorough knowledge of the dynamics of this problem and be his own "psychiatrist."

Since many of these patients have emotional conflicts which are repressed, hypnosis offers more rational approach than most of the currently utilized methods of treatment, either eliciting the underlying psychogenic factors responsible for the nausea and vomiting, or by raising the vomiting threshold of the patient. Since relatively weak suggestion has been partially effective in bringing relief, a type of psychotherapy, combining the use of more powerful suggestion as the main implement, would seem desirable for treating this condition. Such a method where such suggestion can be used is available in the form of hypnosis as used in medicine today. The use of hypnosis is ameliorating subjective sensations of an unpleasant nature has been shown for many years to be an effective form of therapy in medicine.

Certain functional disorders, especially in obstetrics and gynecology, as shown by Kroger and his associates,[9, 10] lend themselves remarkably well to this form of therapy and should command the attention of the obstetrician. Because many of the successful results in treating the nausea and vomiting of pregnancy are obtained on the basis of suggestion, we have selected this condition for the possibility of demonstrating relief through hypnotism by means of which powerful and concentrated suggestion may be easily applied. We wish to emphasize that hypnosis alone is only a means toward treatment and, when combined with only a moderate degree of psychoanalytic skill and knowledge, it can be a much more rapid and effective treatment of hyperemesis gravidarum than any of the n ethods in use today. The intricate methods of Freud and the modern psychoanalytical school are seldom needed. Muniz,[11] Bramwell,[12] and other investigators have used this form of therapy successfully.

Methods and Results

Cases Treated by Hypnosis and Posthypnotic Suggestion

The following procedure was used in seventeen cases. After rapport, which may be defined as the dependence of the subject upon the operator, is established with the patient, hypnosis is induced. This is characterized by a state of gen-

eralized hypersuggestibility which may be two to five times that of the normal waking state. The technique and various states of hypnosis have been described by Estabrook,[13] Erickson,[14] Brenman and Gill,[15] Dorcus and Shaffer,[16] Schilder and Kauders,[17] and Young.[18-20] Several excellent reviews of the literature on hypnosis and suggestion have been published.

The actual induction of the hypnotic trance is a simple procedure. A discussion of what the therapist intends to accomplish is a prerequisite to the actual induction. The therapist, speaking in a confident and monotonous tone, urges the patient to relax. Kraines,[21] technique is as follows: "I want you to relax. Relax every part of your body. Now when I pick up your hand I want it to fall as a piece of wood without any help from you. (The examiner then picks up the hand and lets it drop to the couch.) No, you helped raise the hand that time; just let it be so relaxed that you have no power over it. (The test is repeated as often as is necessary for the patient to learn to let it drop.) That's the way. Now relax your legs the same way; just let them be limp. Now take a deep breath and let it out slowly. Now concentrate on your toes. A warm sensation starts in your toes and sweeps up your legs, abdomen, chest, into your neck. Now relax your jaws. Relax them more, still more. Now your cheeks; now your eyes. Your eyes are getting heavier and heavier. You can hardly keep them open. Soon they will close. Now smooth out the wrinkles in your forehead. Good. Now make your mind a blank. Allow no thoughts to enter. Just blank. You see a blackness spreading before you. Now sleep. Sleep. Sleep. Sleep. Your entire mind and body are relaxed, sleep, sleep. (This phrase is repeated several times in a soft and persuasive voice.) Your sleep is becoming deeper, still deeper. You are in a deep, deep, sleep." After two or three minutes of monotonous repetition of the above suggestions, the patient is told to raise her arm and that it will become very rigid. This state is called cataleptic. It is the most effective state for therapeutic suggestion.

The susceptibility to hypnosis is determined by at least three factors:

(1) The subject's previous experience.
(2) The hypnotist's ability.
(3) The method of induction.

These three variables account for the wide divergence in statements made. Serog[22] claims that 100 per cent of normal healthy men and women are susceptible to some form of hypnosis. In our experience, comprising several thousand cases of hypnosis, the incidence of success has been about 90 per cent. Nearly all investigators concur that suggestions are more often effective when the patient is in a somnambulistic state, which is a state of complete posthypnotic amnesia. Suggestions are made to the patient in this state that she will stop vomiting. She will ask for food and retain it, not only immediately but for the duration of her pregnancy. These posthypnostic suggestions last for about a month, and when repeated often enough the desired results may become permanent, as has been pointed out by Kellogg[23] and Patten.[24] These posthypnotic suggestions are, as Erickson[25] has described, separate hypnotic states arising spontaneously in the individual. All fifteen cases were relieved utilizing this method. Only

one treatment was necessary to bring relief to five cases, two to six treatments were necessary for ten cases. There were two failures; one patient could not be hypnotized, and in another, although light hypnosis was induced, the vomiting stopped for two days and then recurred, necessitating therapeutic abortion. The following case histories are typical of our methods and results.

Case Reports

Mrs. V. W., No. 237-716, Illinois Research Hospital, aged 29 years, Negro woman, para i, gravida iii, last menstrual period June 4, 1943, at term March 2, 1944; admitted to the Illinois Research Hospital July 26, 1943, with a history of severe nausea and vomiting, accompanied by epigastric pain since July 18, 1934.

The nausea and vomiting resulted in a fifteen pound weight loss. She was extremely nervous, weak, and complained of headaches.

Past medical history was essentially negative. Obstetric history; therapeutic abortion February, 1938, at three months because of severe hyperemesis gravidarum. Second pregnancy resulted in a normal infant at term June, 1939, but the first trimester was accompanied by extreme nausea and vomiting. Physical examination on admittance revealed a patient who was acutely ill with considerable somnolence and lassitude. The skin and conjunctivae had a yellowish tint. Blood pressure 132/94, icteric index 9.0 mg. per 100 c.c. blood, nonprotein nitrogen 24.0 mg. per c.c. blood, weight 108 pounds, and the temperature 99.2° F.

In spite of the usual therapy consisting of dietary restriction, sedation and parenteral fluids, the vomiting persisted. Deep hypnosis, accompanied by somnambulism was induced July 27, 1943, one day after admission. This resulted in a complete and dramatic cessation of the nausea and vomiting and the patient was able to eat her regular diet from then on. Patient left the hospital in excellent condition. Posthypnotic suggestions were given to her while she was in a deep hypnotic state that she would have no more nausea and vomiting, and that she would look forward to having her baby with a feeling of joy and happiness. On October 15, 1943, under hypno-analysis, the patient confessed that she did not desire the pregnancy because of her poor financial condition and the possibility that her husband might be drafted.

On November 12, 1943, she weighed 127, an increase of 19 pounds since her admission on July 26, 1943. She has had no nausea and vomiting since the first induction of hypnosis in the hospital.

Mrs. E. H., No. 17406, Cook County Hospital: Negro woman, aged 30 years, para ii, gravida iii, L.M.P. Jan. 1, 1943. Two previous admissions to the hospital of 35 and 16 days respectively for the treatment of hyperemesis gravidarum during the first two months of pregnancy. On April 11, ten days after release from the hospital, the patient was readmitted with the same symptoms as before. She now appeared acutely ill and moaned continuously because of pain and tenderness in the epigastrium. The reflexes were hyperactive, the blood pressure 140/80, physical findings were otherwise negative. Laboratory findings were as follows: red blood count, 4,350. The urine showed a 1 plus albumin and a trace of acetone. The treatment consisted of parenteral fluids, sedation, vitamins, a gradual increasing diet, and corpus luteum extract intramuscularly. After a few days of this treatment, the urine showed a 4 plus acetone and 1 plus albumin. The patient failed to improve clinically, often being most uncooperative and excitable, vomiting greenish mucous many times daily and feeling very despondent. On April 15, the sclerae became jaundiced, the muscles hyperirritable; she also complained of epigastric pain and a stiff neck. Medical consultation stated that this suggested liver damage. On this day the nitroprotein nitrogen was 27, chlorides 495, uric acid 2.4, calcium 10.2, phosphorus 2.13, icteric index 25, hemoglobin 78 per cent, red blood count 3.99 million, white blood count 10,200; bile was present in the urine. Calcium gluconate and cevitamic acid were added to the other parenteral medications. On April 16, the pulse varied from 80 to 116 and became weak and irregular. The jaundice,

hyperirritability, vomiting, and epigastric pain increased. Immediate therapeutic abortion was considered, but hypnosis was suggested as a last resort.

On this day she was placed in a deep somnambulistic state by one of us (W. S. K.). Strong posthypnotic suggestions were given to her that the vomiting would cease immediately, and that she would be able to eat and retain her meals. She was left in a deep hypnotic state for two hours with her right arm held in hyperextension and cataleptic. She was then awakened, and an obvious and dramatic change in her condition could be seen. Her apprehension and excitability were gone and she stated that she now felt greatly improved. On each of the next two days she retained three or four small feedings and thereafter larger ones. She was hypnotized daily for a total of six times by one of us (W. S. K.) and the intern, to whom rapport had been transferred. She improved steadily. The jaundice cleared up, the icteric index gradually returned to normal, and the pulse became regular. In ten days the patient was up and about and left the hospital in good condition. Thereafter she had an uneventful prenatal course and delivered spontaneously on October 19, 1943.

Cases Treated by Hypno-Analysis and Age Regression

It occurred to us that most cases of nausea and vomiting present a characteristic constitutional psychosomatic pattern which may be responsible for a lowered vomiting threshold. Because latent psychogenic factors contribute to the intensity and production of the more severe cases of vomiting, they must be determined by an exhaustive study of the personality. We have utilized age regression with hypno-analysis, which is a rapid form of psychoanalysis under hypnosis. The technique of hypno-analysis has been described by Hadfield,[26] Karup,[27] and Taylor.[28] The patient is regressed to a preadolescent age prior to the pregnancy. The patient is then slowly reorientated to her present chronological age. The development of emotional conflicts, personality changes, inhibitions, faulty attitudes toward pregnancy, or harmful habit patterns can easily be discovered. Appropriate suggestions are then made toward their removal. After the patient is reeducated by intensive psychotherapy under hypnosis, a cure may be effected readily. However, it must be emphasized again that hypnosis, when used in these cases, is only a means toward treatment, not the cure itself. It only effectively speeds up the entire process. We agree with Kraines[29] who states, "In the therapeutic suggestions it is not only important to suggest that the symptom clear up, but to suggest that the basic emotional difficulties be dealt with. Hypnosis thus becomes a valuable aid in enabling the patient to carry out the retraining of the personality as well as suggesting away the symptoms. Hypnosis which deals only with the symptom cannot obtain permanent remission, and the symptoms will recur until the basic cause of the symptom is removed." We believe that hypno-analysis and age regression can extract and use intimate facts from the subconscious mind which ordinarily would not be available to the physician with the patient in the wakened state.

Four patients were treated by hypno-analysis and age regression. Three to five applications were necessary to elicit the factors responsible for the symptoms of the four cases in our small series. Among the psychogenic factors responsible for the vomiting in one of the cases was an unhappy home life with impending divorce; the threatened loss of a career due to pregnancy was a factor responsible for the vomiting in another case.

The following cases are typical of our methods and results:

CASE 1.—Mrs. E. P., aged 31 years, white, para ii, gravida iii, L. M. P. June 22, 1941. On August 26, when about two months pregnant, she complained of severe nausea and vomiting. Physical examination was essentially negative. Past obstetric history: two normal full term pregnancies, with no nausea or vomiting during either pregnancy. Usual therapy consisting of dietary restriction, sedation, hormones, and strong waking suggestions were of no value. After one week of intractable vomiting, during which time the patient lost 12 pounds, hypnosis was induced on September 2, 1941, and repeated on September 5. The usual posthypnotic suggestions were given. The urine showed acetone 1 plus, albumin 0. Patient returned two days later and stated that she felt worse. At this time deep hypnosis was induced, and the patient regressed to the age of 30. The following salient facts were elicited. She was not in love with her husband and was extremely frigid during sexual intercourse with him. On numerous occasions during the past two years, she had extramarital relations with another man, with whom now she was very much in love. While in the hypnotic state she admitted that this man was responsible for this pregnancy. Under hypnosis it was made clear to her that the vomiting was a rejection of the pregnancy. Because she had divulged material that had been repressed, her strong guilt feelings would now disappear, and her secret would never be disclosed. She was reorientated to her present chronological age and awakened. As a result of this "mental catharsis" she felt very much relieved. Her nausea and vomiting promptly ceased the following day, and the remainder of her prenatal period was uneventful.

The above information could no doubt have been elicited without hypno-analysis, but it might have taken considerable time. The rapid cessation of the nausea and vomiting cannot be explained on any other basis.

CASE 2.—Mrs. J. K., aged 28 years, white, para 0, gravida i, L. M. P. April 15, 1942, at term January 22, 1943, had a history of nausea and vomiting of one week duration. On July 17, deep hypnosis was induced and posthypnotic suggestions were given that all nausea and vomiting would disappear. The patient returned in one week and stated that her symptoms, although milder, were still present. On January 24, deep hypnosis was again induced and the patient regressed to the age of twelve. The following facts were elicited: she had been a tomboy as a young girl and wished she had been a man. She married only because her family wished her to, and was not in love with her husband. Intercourse was extremely distasteful to her. It was only at her husband's wish that she became pregnant. She detested dressing up in feminine clothes, preferred slacks and mannish attire. Consciously, she denied any homosexual tendencies. Under hypnosis, induced on August 2, she stated that the reason for the nausea and vomiting might be due to the repudiation of her femininity and rejection of the pregnancy. The nausea and vomiting persisted. Under hypnosis on August 15, she agreed to give up her unconscious masculine tendencies and accept the child. The nausea and vomiting ceased and the remainder of her prenatal period was uneventful.

Discussion

In our series of 21 cases treated as described above, utilizing hypnosis as a method for controlling the neurotic tendency of the nausea and vomiting of pregnancy, the results are most gratifying.

Most of the patients were affected seriously enough to require hospitalization. No definite reason could be demonstrated for the vomiting. The usual methods of treatment consisting of dietary restriction, sedation, and parenteral fluids relieved the dehydration and inanition, but did not control the vomiting. One case (E. H.) described above, was so severe that immediate therapeutic abortion was considered.

The inconvenience of using hypnosis is relatively negligible when compared with other time-consuming therapeutic methods. The technique of hypnosis can easily be acquired by any physician. The mechanism of it's therapeutic action in these cases is either that underlying etiological factors are discovered and effectively removed by suggestion, thereby raising the vomiting threshold, or else hypnosis and posthypnotic suggestion may establish a block in the nervous pathway between the gastrointestinal tract and the vomiting center in the higher sensorium. Heyer[30] has demonstrated the effect of hypnotic suggestion on peristaltic movements of the intestinal tract, and these can either be augmented or abolished. One of the explanations for this block may be that the effect of hypnosis is "synaptic ablation," states Estabrook.[31] Kroger[32] induced vomiting in normal patients previously conditioned by hypnosis; thus the entire vomiting syndrome of pregnancy can be reproduced by posthypnotic suggestion. This is additional evidence that hyperemesis gravidarum is hysterical in nature.

Hull[33] states, "Through hypnotism, one may have an effective control of the high centers and certain processes only feebly influenced by voluntary effort. These are possibilities that the ready control of such physiologic mechanisms might prove of value in the treatment of numerous somatic disorders." Evidence which demonstrates the effect of hypnosis in these conditions would probably require a more thorough type of investigation. From a practical standpoint, however, hypnosis offers a very valuable method to our obstetric therapeutic armamentarium in bringing relief to a group of patients who suffer considerably during pregnancy. This fact alone warrants extensive trial with hypnosis.

Our experience substantiates Estabrook's[34] contention that, "One of the most useful of all hypnotic phenomena, at least from the viewpoint of medicine, is that curious ability which the somnambulist has to recall long forgotten memories. This is the keynote to hypno-analysis, a branch of psychotherapy which is destined to assume more and more importance as the prejudice to hypnotism in this country diminishes. Hypno-analysis is slowly coming into its own. It is a tremendous timesaver."

Hypno-analysis and age regression elicit latent psychogenic factors from the subconscious mind which are responsible for the nausea and vomiting. In addition, the patient may be unaware of these or have no desire to tell them to the physician. By this means, the attention can also be directed to a given topic so that more ideas related to the causative factors may be elicited through the processes of association, thus facilitating the searching out of the vomiting complex and allowing the patient more insight for the causation of her symptoms . . . the process of reintegration. In several articles, the thorough work of Erickson,[35, 36] comprising several thousand cases, has shown that, in competent hands, there should be no untoward reactions or risk following the use of hypnosis. The prejudice which has relegated hypnotism to obscurity as an unexplained phenomenon, and which may have been warranted years ago because of unscientific activities should now be

abolished, and an objective evaluation made of the use of this valuable form of treatment. In addition, through controlled experiments that were not available to the earlier investigators, much more can be learned regarding its therapeutic application.

Summary

Nineteen cases of nausea and vomiting of pregnancy of varying intensity, ranging from the exaggeration of physiologic vomiting to true hyperemesis gravidarum, who obtained little or no relief following a wide variety of symptomatic treatments, were completely relieved of their subjective symptoms following the use of hypnosis, either with direct suggestion or with hypno-analysis and age regression. All patients except two were completely relieved utilizing these methods.

This form of therapy may act either by raising the vomiting threshold directly or by preventing contractions from the gastrointestinal tract reaching the higher sensorium. Again, the method of eliciting latent psychogenic factors responsible for the nausea and vomiting and bringing these to the surface and integrating them into consciousness is also a convenient, time-saving, and most effective therapeutic procedure for permanently relieving this ordinarily refractory condition.

We believe that this valuable adjunct in the treatment of the nausea and vomiting of pregnancy should be utilized by obstetricians.

We wish to express our thanks to Dr. Fred H. Falls for the use of the clinical material and to Dr. William J. Dieckmann and Dr. J. P. Greenhill for the valuable assistance they rendered in the preparation of this manuscript.

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THE MECHANISM OF THE HISTIDINURIA OF PREGNANCY*

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SINCE Voge[1] first noted the histidinuria of normal pregnancy in 1929, over 100 medical articles have dealt with this subject. Most of these reports were stimulated by the work of Kapeller-Adler, who improved Knoop's bromination reaction[2] for urinary histidine and urged its employment as a chemical test for pregnancy.[3, 4] Subsequent studies have shown beyond doubt that the iminazole compound excreted is actually l-histidine,[5, 6] and that much larger quantities of this essential amino acid are excreted during pregnancy, at least from the eighth to the thirty-sixth week after conception, than in the non-pregnant state.[7, 8]

It is evident that routine qualitative tests for histidinuria can never become an accurate means of diagnosing pregnancy, for, with refinements of technique, almost all urines become "positive" for histidine, and the concentration of histidine is influenced by the diet,[8] by the specific gravity of the urine,[10] and by the duration of pregnancy.[7] Of greater interest would be the determination of the cause of the histidinuria, for this would furnish a basis for studying the reasons for its disappearance when pre-eclampsia or eclampsia supervenes.[11]

Possible Causes of the Histidinuria

The only serious explanation of pregnancy histidinuria which has been advanced is that of Kapeller-Adler and her co-workers. In a series of articles, she showed that only the human species excretes histidine during pregnancy;[12] that liver tissue removed from pregnant women at autopsy does not readily metabolize histidine, while specimens from men or non-pregnant women—even those showing extensive liver damage—show marked histidase activity;[13] and that the addition of 50 to 500 rat units of chorionic gonadotropic hormone to ground human liver in vitro inhibits histidase activity.[14] She believes, therefore, that this placental hormone which is produced only by the human species inhibits the normal metabolic breakdown of histidine by the liver, thus resulting in its excretion. More recently, she has suggested that histidine disappears from the urine in pre-eclampsia because a large proportion of it is transformed by a tissue decarboxylase to histamine, and that the latter may be a cause of the toxemia.[15, 16] Some doubt is cast upon these concepts when it is realized that the chorionic hormone does not show an in vitro inhibition of purified histidase,[14] and that when the excretion of the hormone is at its peak in early pregnancy, the rate of histidine excretion may be very low in-

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†With the technical assistance of Miss Dean Mayell.

deed.[7] Furthermore, Edlbacher and Heitz[17] have been unable to confirm the relative inactivity of histidase in the liver tissue of pregnant women.

Instead of postulating any alteration of histidine catabolism in pregnancy, it is possible that the histidinuria could be due to a "lowered renal threshold," that is, to an inhibition of the tubular reabsorption of histidine. If this were true, then the administration of histidine orally or intravenously should result in its excretion at normal or low blood levels. If the liver histidase were inhibited, on the other hand, then the administration of histidine should result in a greater and more prolonged rise in the blood level. The present study is an examination of these two hypotheses.

Measurement of Blood Histidine

While the bromination technique is specific for the iminazole ring, it is not sensitive enough to detect the low concentrations found in blood. The diazo reagents such as p-phenyldiazonium sulfonate (Pauly's reaction), and diazotized p-nitroaniline or p-chloroaniline produce strong colors with both phenolic and iminazole compounds, and the diazo color of blood filtrates has often been attributed to "blood phenols." Barac[18, 19] and Schwarz and coworkers[20, 21] have shown quite convincingly that the diazo color of blood is due almost entirely, if not exclusively, to histidine, and that the concentration in normal blood serum is about 1.5 to 2.0 milligrams per cent. Regardless of its origin, we have for the purposes of this study considered the initial fasting blood level as a blank, and deal only with those increases which followed the administration of pure histidine.* We adopted p-chloroaniline, the reagent suggested by Edlbacher and his associates,[22] and found that reliable results were given by a perchloric acid filtrate[23] of whole blood. Because the color development is influenced by other blood constituents, as well as by the pH and temperature, we always determined for each sample the increment of color produced by adding 0.05 mg. of pure histidine to an aliquot portion.

Method

Reagents:

1. Diazo Solution I: 0.5 Gm. p-chloroaniline and 5 ml. concentrated hydrochloric acid diluted to 200 ml. with distilled water.
2. Diazo Solution II: 0.5 per cent solution of sodium nitrite.
3. Diazo Reagent: mix 2 parts of solution I with 1 part of solution II just before use.
4. M/20 Sodium Carbonate: 0.53 per cent solution anhydrous sodium carbonate.
5. Histidine Standard: 6.175 mg. of l-histidine mono-hydrochloride in 100 ml. of 0.1 N sulfuric acid.

All reactions must be carried on with solutions which are below 5° C.

Procedure:

1. Dilute 5 ml. whole blood with 10 ml. distilled water, add 10 ml. 4.4 per cent perchloric acid, shake well and centrifuge.
2. Adjust the pH of 5 ml. of the supernatant fluid to 8.0 ± 0.1 with sodium hydroxide. Cool below 5° C.
3. Add 5 ml. of cold sodium carbonate solution and then 0.5 ml. of the diazo reagent drop by drop while shaking.

*The l- and d-histidine used in these studies was generously supplied by Mr. E. A. Wickham of the Hoffmann-La Roche Company.

4. Allow mixtures to stand in the ice bath for exactly three minutes, then add 10 ml. of butyl alcohol and shake vigorously.

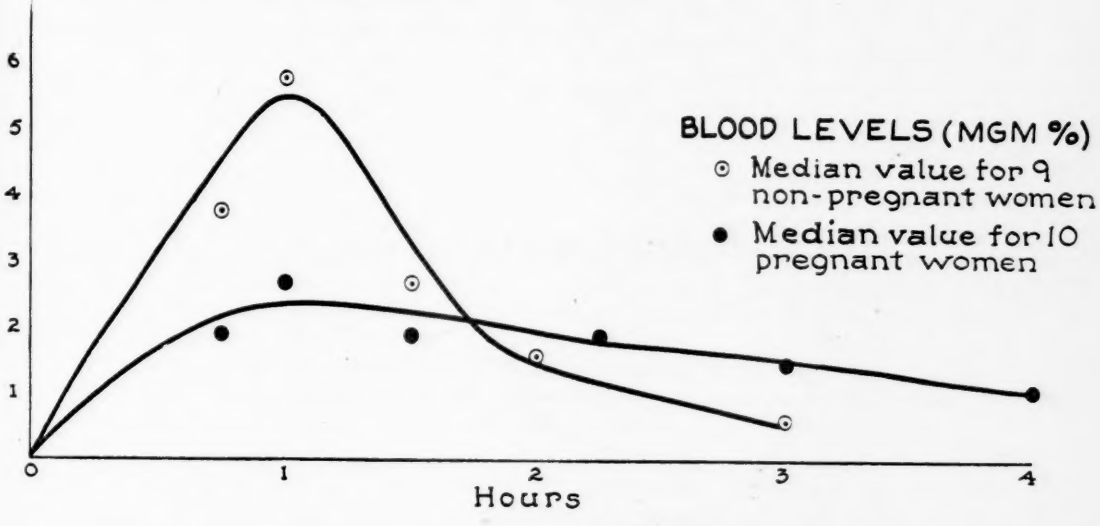
5. Centrifuge and pipette off the butyl alcohol fraction.

6. Run a standard (consisting of 1 ml. of histidine standard solution to 5 ml. of filtrate) and a reagent blank at the same time.

7. Measure with a green (No. 54) filter in a Klett colorimeter, setting the zero reading against the reagent blank.

The Measurement of Histidine Excretion Rates

In all cases, a preliminary urine collection of known duration was obtained, and patients were instructed to drink one glass of water or lemonade every hour during the test. Following the oral administration of histidine, voided specimens were obtained at stated intervals, but following intravenous administration, hourly samples were collected by the use of an indwelling catheter. Because of the inherent errors of urine collections, especially during pregnancy, creatinine determinations were made by the method of Peters,[24] and the time intervals were adjusted by assuming a constant hourly creatinine excretion for any one individual.[25] In this way, an incomplete emptying of the bladder would not affect the final rate calculations. The urinary concentration of histidine was determined by our method previously published,[7] and expressed as the quantity of histidine base excreted per hour or for an 8-hour period.



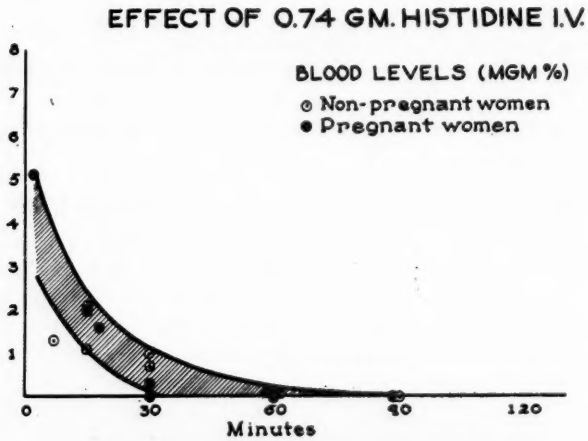
HISTIDINE EXCRETION (MGM)

	No. Cases	8 hour period before histidine	8 hour period after histidine
Non-pregnant women	9	Range 0 - 54 Median = 23	Range 35 - 145 Median = 80
Pregnant women	10	Range 40 - 156 Median = 88	Range 84 - 550 Median = 314

Fig. 1.—Effect of 3.0 Gm. histidine orally.

Results

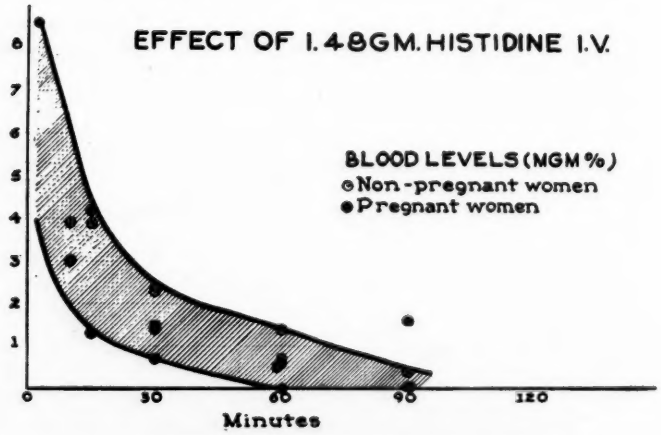
When 4 Gm. of l-histidine hydrochloride (equivalent to 3 Gm. of histidine) are given orally to normal fasting nonpregnant women, there is a progressive rise in the blood histidine followed by a slower decline as illustrated in Fig. 1. For any one individual the



HISTIDINE EXCRETION (MGM/HOUR)

Pregnancy	Before histidine	After histidine		
		1st hour	2nd hour	3rd hour
Not pregnant	1.4	2.8	1.8	0.7
Not pregnant	14.0	46.0	13.0	—
Not pregnant	0.	4.2	0.	0.
20 weeks	1.6	47.8	13.0	—
39 weeks	15.0	90.0	30.0	28.0

Fig. 2.



HISTIDINE EXCRETION (MGM/HOUR)

Pregnancy	Before histidine	After histidine		
		1st hour	2nd hour	3rd hour
Not pregnant	1.5	22.2	0	0
Not pregnant	2.2	25.0	15.0	14.0
28 weeks	1.3	25.2	17.0	13.0
32 weeks	10.3	48.5	33.0	—
35 weeks	50.0	262.0	41.0	—

Fig. 3.

rise and fall forms a smooth curve, but because the peak is attained at slightly different times in different persons, the median values do not fall exactly on the composite curve which is reproduced in Fig. 1. Nevertheless, there is a consistent difference between the blood curve of a nonpregnant and a pregnant woman, which is well illustrated by these average values. In normal pregnancy, the blood level rises more slowly, remains lower and persists for a longer period of time. That this is a characteristic of pregnancy is further emphasized by the fact that we have, in six additional cases, observed a gradual transition to the nonpregnant type of curve and to the lower excretion rates during the first eight days of the puerperium. At first glance, it might seem that this would indicate an altered rate of histidine metabolism during pregnancy, but it is obvious that the observed difference could just as well be due to a delayed absorption from the gastrointestinal tract. Indeed, the results of intravenous administration to be described below indicate that such is the case.

The significant finding from these experiments is that *a much higher rate of histidine excretion occurred at the same or even at lower blood levels in pregnant women.* This could mean only one thing, namely, that there is a "lowered renal threshold," or in other words, a diminished reabsorption of the amino acid by the renal tubules. As one may see from the data in Fig. 1, even the lowest excretion rate observed in pregnancy exceeds the average rate for nonpregnant women.

In order to differentiate between gastrointestinal and metabolic changes, several experiments were conducted wherein l-histidine was administered intravenously. A 10 per cent solution of l-histidine hydrochloride in saline was adjusted to pH 6.5, sterilized with a Seitz filter and given as a single rapid intravenous injection. No subjective symptoms or alterations of pulse rate or blood pressure have been noted.

Like the experiments conducted on dogs by Leiter,[26] the injected histidine disappears rapidly from the blood stream. Only a small proportion appears in the urine, showing that the greater part is utilized or destroyed. As illustrated in Figs. 2 and 3, the amino acid disappears *with equal rapidity in both pregnant and nonpregnant women.* If anything, the results of giving the larger dose of 1.48 Gm. by vein show a slower disappearance in nonpregnant women, though the cases are too few to establish this point. The ranges of blood levels as illustrated by the shaded areas include all but one or two aberrant values. With the larger dosage (Fig. 3) the shape of the curve is similar, but the blood levels are higher and persist longer.

If l-histidine is distributed in the extracellular fluids of the body-like galactose,[27] thiocyanate,[28] and similar substances, then an analysis of our data indicates that this equilibrium is rapidly attained within 10 to 15 minutes after intravenous injection. Some of the variations in blood levels are due to differences in body weight, but these variations cannot be correlated with the presence or absence of pregnancy. There is nothing in these data to support the contention that liver histidase is inhibited during normal pregnancy.

While there is an individual overlap, the highest excretion rate of 262 mg. in one hour occurred during normal pregnancy, and when allowance is made for the initial control rate, this represents an excretion of 15 per cent of the amount injected. The high rates in pregnancy and the lowest rates in nonpregnant women were observed at the same blood levels, again indicating an alteration of the renal threshold.

Discussion

Under normal circumstances, amino acids are freely filtered by the glomeruli and almost totally reabsorbed by the renal tubules. Doty[29] found that the dog's kidney reabsorbs 99 per cent of the histidine which passes into the glomerular filtrate. Pitts[30] believes that there is a specific mechanism for amino acid reabsorption and that such substances as creatine compete with certain amino acids for reabsorption. Our results indicate that pregnancy histidinuria is due to a diminution in this tubular reabsorption and not to a reduced rate of catabolism or utilization.

Is this phenomenon specific for l-histidine, or is it true of other amino acids? In some work to be reported later, we have observed that when the optical isomer d-histidine is injected, very high excretion rates result, but they are the same in both pregnant and nonpregnant women. The blood curves, showing a very slow metabolism of this unnatural substance, are likewise the same. We have administered 4 Gm. of tyrosine to pregnant women, but in this case there is no detectable excretion of tyrosine at all. It would seem, therefore, that the diminished tubular reabsorption for l-histidine does not apply to all related substances.

The histidinuria of pregnancy could then be due to a selective inhibition of the tubular reabsorptive mechanism, or to the competition of some other substance (such as the metabolite of a hormone) for reabsorption by this same mechanism. On this point we have no data, so that the immediate cause of the alteration in tubular function is as yet undetermined.

The work of Eiler, Althausen, and Stockholm[31] has shown that a hormone (thyroxin) can alter markedly the rate of absorption of glucose, or other substance transferred by an active mechanism, from both intestinal or renal tubular epithelium. The present data indicates that l-histidine, which is also absorbed by an active mechanism, has a slower rate of transfer across both the intestinal and renal tubular barriers during normal pregnancy, and it is entirely possible that some hormonal change is responsible for both effects.

Summary

Simultaneous blood levels and urinary excretion rates of l-histidine were studied after its oral or intravenous administration. When given by vein, the histidine disappears from the blood stream with equal rapidity in both pregnant and nonpregnant women, which suggests that there is no interference with its utilization or destruction during gestation. Pregnant women, however, excrete a larger proportion of the histidine at the same or even at lower blood levels, demonstrating a "lowered renal threshold." When given orally, the same increased excretion rate at lower blood levels is noted during pregnancy, but the blood curves indicate a delayed absorption from the gastrointestinal tract. The decreased rate of absorption from both the gastrointestinal mucosa and the epithelium of the renal tubules observed in normal pregnancy may be due to the same inhibitory factor.

Pregnancy histidinuria has been attributed in the past to a hormonal inhibition of liver histidase. The experiments which we describe, however, support the alternative hypothesis that it is due to an inhibition or interference with the renal tubular reabsorptive mechanism for this particular amino acid.

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GRANULOSA-CELL TUMOR OF THE OVARY

Report of Five Cases With Premature Menopause (Amenorrhea) and the Recurrence of Menstruation

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ONE of the most impressive ovarian tumors is the granulosa-cell tumor. Although, since 1931, numerous articles have appeared in the scientific journals describing the tumor and its symptomatology, it is hoped that this report is not too repetitious. After removing a large granulosa-cell tumor of the ovary from a woman who had started menstruating again after an eight-year period of amenorrhea, the author decided to review the literature and study our records of University Hospitals in regard to certain aspects of this neoplasm. No detailed survey of the literature is given since there are already adequate reports in the journals.

To date, numerous articles and some 240 cases have appeared, many of which are individual case reports. The eagerness to report isolated cases is well understood when one considers the striking symptoms that often accompany this tumor. Especially is this true with granulosa-cell tumors in children.

Only twenty-one cases of granulosa-cell tumors were found in the records of the University Hospitals of Cleveland, and of these twenty-one cases, only two were diagnosed histopathologically as malignant.

Uterine changes most commonly mentioned with the granulosa-cell tumor are hypertrophy of the uterine musculature and hyperplasia of the endometrium. All of our cases in which the uterus was removed or in which a curettement was done showed these findings.

In dealing with a tumor such as the granulosa-cell type in which the three age periods reveal different types of symptoms, one can arrange the patients in three groups: (1) prepubescent or childhood (from infancy to puberty); (2) pubertal-adult (from puberty to menopause); (3) postmenopausal. The second group includes the period when normal menstruation would take place. This report is most concerned with the second group, although four cases in the third or postmenopausal group are mentioned. None of our cases fall into the first group, since we had no case less than 23 years of age.

The frequency with which granulosa-cell tumors occur as to decade in our twenty-one cases is similar to figures found in the literature. All agree that granulosa-cell tumors occur most frequently after menopause. Distribution of our twenty-one cases according to decade is as follows: 2 cases (9.5 per cent) in the 3rd decade; 9 cases (42.0 per cent) in the 4th decade; 7 cases (33.3 per cent) in the 5th decade; 2 cases (9.5 per cent) in the 6th decade; 1 case (4.7 per cent) in the 7th decade. The youngest patient in our series was twenty-three and the oldest sixty-nine.

In reviewing our case records, we were surprised to find five (23.8 per cent) of our patients gave a history of premature menopause (amenorrhea), followed by return of menstruation. Menstruation is used here as "uterine bleeding" regardless of whether it is normal menstruation or not. Hyperestrinism, as mentioned before, produced by the granulosa-cell tumor apparently accounts for the prevalent symptoms of menorrhagia or metrorrhagia (hypermenorrhea) or with the long periods of amenorrhea (polyhormonal amenorrhea).

Report of Cases*

CASE 1.—R. H., a 43-year-old Negro woman, was admitted to the gynecologic service of University Hospitals on April 3, 1944, with the complaint of profuse vaginal bleeding. In 1933, at the age of 35, she had stopped menstruating. At that time she experienced "hot flashes," dizziness, and other menopausal symptoms. In April, 1943, about one year before admission to the hospital, she began to menstruate again. This was irregular at first, with periods often lasting for one month. From November, 1943, bleeding continued throughout both November and December. With only three weeks' freedom from bleeding, menstruation again reappeared in the latter part of January and continued until operation. However, the patient was discharged from the hospital and remained home until readmission on July 9, 1944, to "gain strength and deliberate over the advised operation." One transfusion was given before she left the hospital. Aside from pelvic and abdominal findings and anemia, the patient was normal. Pelvic examination showed a large tumor mass the size of a four months' pregnancy. There was tenderness over the abdomen, but no rigidity or muscle spasm. No other suggestion of adnexitis was found. Temperature, 37.8° C.; pulse, 100, respiration, 20, blood pressure, 130/80.

Readmission: July 9, 1944: temperature, 37.4° C.; pulse, 84; respiration, 20; blood pressure, 130/80. Examination showed the same findings as described on her previous admission, but there was marked increase in size of the mass. Abdomen was extremely tender, and on the second day following a routine intravenous pyelogram her temperature rose to 40° C. She appeared extremely ill. Blood Count: white blood cells, 7,200; red blood cells, 2,630,000; hemoglobin, 58 per cent (Sahli). Urinalysis and microscopic precipitation test were negative. X-ray studies of kidney pelvis showed no radiologic evidence of a process of the upper urinary tract. Flat plate revealed rudimentary ribs on Lumbar 1 bilaterally. The neural arch of Sacral 1 was incompletely fused.

The patient's condition grew steadily worse, with the onset of nausea and vomiting. She refused to take food. The rise in temperature was concomitant with the complaint of "severe pain" in her abdomen. A rather sudden enlargement of the tumor mass followed the pre-x-ray routine of castor oil catharsis, precipitating the onset of fever, pain, and nausea, vomiting and marked enlargement of her abdomen.

On July 18, 1944, operation was scheduled for the following morning, and it was felt that the exacerbation of her condition was due to hemorrhage into a large ovarian tumor. On July 19, 1944, she was taken to the operating room and a large right ovarian tumor was removed. It measured 19 by 17 by 9 cm., and weighed 1,670 grams.

Pathologic Report.—"Granulosa-cell tumor of ovary, the seat of extensive necrosis, acute inflammation, and recent hemorrhage." The subsequent hospital course was uneventful, and she was discharged on the 11th postoperative day. She was given two transfusions of whole citrated blood, 500 c.c. each.

CASE 2.—S. R., a 45-year-old white woman, entered the gynecologic service as a private patient of Dr. R. L. Faulkner. Her complaint was vaginal bleeding for six months. She also gave a history of pain in her right side during the six months following the onset of her bleeding. Menstrual history: menarche at 16 years of age, regular every 28 days

*Case 5 is listed both as granulosa-cell tumor and theca-cell tumor.

to 30 days, with a period of amenorrhea for six and one-half years prior to the remenstruation that brought her to the hospital. The laboratory findings were essentially negative.

Examination on October 16, 1939, under evipal anesthesia, revealed hypertrophy of the posterior lip of the cervix with many nabothian follicles in its substance, and a tumor mass about the size of an orange on the right side. There were no other abnormalities.

On October 17, 1939, excision of the labial cyst, panhysterectomy, right salpingo-oophorectomy, and left salpingectomy were done.

Pathologic Report.—"Granulosa-cell tumor of ovary, follicular type. Physiologic hyperplasia of endometrium, mild. Chronic cervicitis. Hydrosalpinx, bilateral."

The hospital course was uneventful, and the patient was discharged on her thirteenth postoperative day.

CASE 3.—F. D. (patient of Dr. W. H. Weir), a 40-year-old white woman, entered the gynecologic service on August 7, 1940, with the complaint of menorrhagia following a period of two years of amenorrhea. Her menstrual history was normal, with menses occurring every 28 days until 1937, when amenorrhea was sudden. Seven weeks before admission bleeding started and had been continuous until operation.

On August 8, 1940, a panhysterectomy, bilateral salpingo-oophorectomy and appendectomy were done. The postoperative course was uneventful and the patient was discharged on the fourteenth postoperative day.

Pathologic Report.—"Granulosa-cell tumor of ovary. Fibromyoma of uterus. Adenomatous polyp of the endocervix. Chronic cervicitis. Fallopian tube—no pathologic diagnosis. Appendix—no pathologic diagnosis." The tumor (ovarian) measured 9 by 6 by 5.5 cm. and weighed 65 grams.

CASE 4.—L. T. (staff service), a 23-year-old Negro woman, entered the gynecologic service on June 14, 1937, with the complaint of a rapidly enlarging abdominal tumor, a 70-pound weight loss during the preceding 18 months, and profuse vaginal bleeding during the preceding year which often lasted for a month. Prior to onset of her present illness, she experienced eight months of amenorrhea.

The patient was extremely emaciated, weak, and severely anemic. Temperature 38.2° C.; pulse, 100; respiration, 25; blood pressure, 150/90. She had a slightly enlarged heart with loud systolic thrill at apex and systolic and diastolic murmur over pulmonic area. There was an irregular mass in the lower right quadrant and a definite fluid was imparted to the palpating hand. There was hydronephrosis of the right kidney and marked displacement of intestines and of kidneys. The amount of abdominal fluid was increased. X-ray examination of chest showed both diaphragms to be high in position, and a small soft shadow of increased density in the right first interspace just below the clavicle. Laboratory findings: admission white blood cells, 5,500; red blood cells, 3,110,000; hemoglobin, 30 per cent; phenolsulfonphthalein test, 80 per cent in two hours. On June 17, 1937, 1,500 c.c. of serosanguineous fluid was removed by abdominal paracentesis; this was negative for tuberculosis in guinea pig injection. The patient was given two transfusions prior to operation. The amount given was 1,250 c.c. whole citrated blood. On June 24, 1937, a perineorrhaphy, panhysterectomy, bilateral salpingectomy, and left oophorectomy were done under nitrous oxide and ether anesthesia. The tumor (ovarian) weighed 1,200 Gm.

Pathologic Report.—"Granulosa-cell tumor of ovary with cystic degeneration. Physiologic hyperplasia of endometrium. Chronic cervicitis."

After operation, the patient's condition improved. Her hospital course was uneventful, and she was discharged on her eleventh postoperative day.

CASE 5.—R. M. (surgical service, private patient of Dr. F. S. Gibson), a 40-year-old white woman, entered University Hospitals on May 19, 1942, with the complaint of resumption of bleeding after a period of eight years of amenorrhea. Patient was para vi, gravida vi. Aside from her menstrual history, her past history was essentially negative. Her menses began at 12 years of age, being regular and normal in amount until she was 26 years old. At that time they became irregular for a period of six years, then ceased

entirely. Five months before admission to the hospital she began to flow; this was intermittent with spotting almost daily. She had no pelvic or abdominal discomfort.

The significant physical findings were seborrheic dermatitis around the eyes, and cervical lymphadenopathy below old scar on right side of neck where previous draining sinus was present. Pelvic examination was not on record.

On May 20, 1942, under nitrous oxide and ether anesthesia, a supracervical hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were done. The left ovary was cystic, and many adhesions were encountered, making the operation quite difficult.

Pathologic Report.—"The ovarian tumor measured 8 by 6.5 by 4 cm. and weighed 120 Gm." Histopathological report was "Atypical cystic hyperplasia of endometrium. Fibromyoma of uterus, theca-cell tumor and tuberculosis of one ovary. Atrophy of other ovary. Bilateral tuberculous salpingitis and unilateral hydrosalpinx. Appendix—no pathologic diagnosis."

Laboratory findings on admission: white blood count, 7,900; hemoglobin, 65 per cent. Urine was normal. Microscopic precipitation test was negative. Total proteins, 6.87 Gm. per cent; plasma protein, 3.75 Gm. per cent; globulin, 3.15 Gm. per cent.

The hospital course was uneventful, and the patient was discharged on her fourteenth postoperative day.

Comment

There are four patients in the series whose ages are 47, 46, 53, and 69 years in the charts reviewed. All four had reached menopause and experienced postmenopausal bleeding. The intermenstrual period of menopausal amenorrhea was 2 years, 3 years, 3 years, and 20 years respectively in the foregoing cases. All had granulosa-cell tumors.

We have presented the number of cases of granulosa-cell tumors found at the University Hospitals of Cleveland during the past ten years. The review of these cases was prompted by the finding of a recent case in which premenopausal amenorrhea occurred for a period of five years, after which menstruation recurred, making hospitalization necessary.

In reviewing the twenty-one cases of granulosa-cell tumors, we found nine cases of granulosa-cell tumors with a history of amenorrhea followed by remenstruation. This is an incidence of 42.8 per cent. Five patients were classed as having premenopausal amenorrhea, or an incidence of 23.8 per cent. Four of the cases were classed as postmenopausal bleeding, or an incidence of 19.05 per cent.

That this phenomena of amenorrhea followed by menstrual return is the result of hormonal disturbance, has long been known. However, the exact mechanics of the amenorrhea in women who are far from their natural menopause, with a subsequent menstrual flow calls for further enlightment. Klaften states that the prolonged amenorrhea is due to the structures similar to corpus luteum or albicans in the tumor. As far back as 1930, he discussed the possibility for the first time of the enormous hormone activity of granulosa-cell tumors. At that time, he had no case to refer to, but, in 1934, he observed and cited a case of his own in which precocious adolescence in a 4-year-old child occurred with a granulosa-cell tumor.

The age incidence in twenty-one cases was as follows: 51.5 per cent in the third and fourth decade, 33.3 per cent in the fifth decade, 9.5 per cent in

the sixth decade, and 4.7 per cent in the seventh decade. The youngest patient in our series was twenty-three and the oldest sixty-nine.

The ages of the five cases reported were as follows: 43, 45, 40, 23, and 40 years of age.

Conclusions

1. A brief review of the literature has been presented, with a summary of five cases of granulosa-cell tumor from our own case records.

2. The five cases are summarized because of the finding of granulosa-cell tumor associated with premature menopause (amenorrhea with resumption of menstruation).

3. All patients were operated upon. Diagnosis made after operation on gross and by histologic means. Some only after microscopic examination.

4. From the total of twenty-one cases appearing on record, only two were diagnosed as granulosa-cell carcinoma.

5. Granulosa-cell tumors were catalogued according to age groups, namely: (1) prebuscent or childhood, (2) adult (those within the range of normal menstruation), (3) postmenopausal.

6. All twenty-one of our cases were in the second or third groups.

7. Case 1, R. H., menstruated twice after removal of granulosa-cell tumor, and at the present time is approximately three months pregnant.

8. Follow-up studies showed: all patients are living and have no evidence of recurrence.

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INFECTIOUS MONONUCLEOSIS COMPLICATING PREGNANCY

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MRS. R. H. D., para i, gravida iii, first presented herself for obstetric care on Sept. 5, 1944. Past history revealed acute nephritis following scarlet fever in childhood and one instance of surgery: a volvulus at the iliocecal area at the fourth month of the second pregnancy. The first pregnancy was spontaneously aborted after a fall in 1940. Except for the surgery, the second pregnancy was normal in every respect and terminated in full-term delivery in August, 1941.

The patient stated that her last menstrual period was June 27, 1944, and that she had had rather marked nausea and vomiting. General physical examination was negative; her weight was 110 pounds, which represented a loss of 3 pounds. Kahn test was negative; blood type A; red blood cells, 3,870,000 with 70 per cent hemoglobin. Pelvic measurements were adequate. The patient was placed on ferrous sulfate 0.324 Gm. three times a day, and vitamin capsules, and given the usual instructions. She was again seen on October 6 with normal findings except that the red blood count had dropped to 3,320,000 with 62 per cent hemoglobin. At that time the ferrous sulfate was increased to 0.648 Gm. three times a day and 10 units of liver extract (Lederle) were started every other day. After 50 units had been given, erythematous nodes developed about the legs and the medication was stopped.

In the latter part of October the patient spotted for four days and was put to bed. There were no cramps and the uterus appeared to be enlarging normally. Subsequent course was normal, quickening felt on Nov. 15, 1944. The red blood cells and hemoglobin continued to remain somewhat low, ranging from 3,000,000 to 3,600,000, and 56 to 63 per cent, respectively, in spite of the continued large dosage of ferrous sulfate. At the checkup examination on December 28, the patient complained of marked gastric distress, which disappeared when she had, of her own accord, stopped the iron. Lextron was substituted, but this too produced the distress and was shortly discontinued. The patient received no further iron for the remainder of the pregnancy.

On Jan. 28, 1945, the patient complained of marked listlessness. Check-up examination was normal except for a red blood count of 2,890,000 and hemoglobin of 53 per cent. In view of the iron and liver extract intolerance, it was decided to transfuse her. This was done without incident with 500 c.c. of citrated blood, on Feb. 8, 1945, following which the patient felt considerably improved.

Lightening occurred somewhat early, on February 23, the patient experiencing mild pressure symptoms, and moderate hemorrhoids, which persisted throughout the remainder of the pregnancy. On March 10, she complained of marked malaise, listlessness, and anorrhexia. General examination was negative except for a mild temperature elevation (99.6° F. at 2 P.M.), and two moderate-sized hemorrhoids. The pregnancy was enlarging normally, fetal heart 136 in the lower left quadrant, and the head below spine by rectal examination. Urine was negative. Blood count was within normal limits, the transfusion having elevated the red blood cells to 4,100,000. No cause for the slight temperature elevation was discernible.

The patient continued to complain of marked malaise and anorrhexia and became definitely depressed mentally. She was seen frequently, in view of the abnormal course so close to term (April 3, 1945). She stated that it was a marked effort for her to get out of bed. She continued to run an evening temperature elevation, usually to about 100° F., and, on occasion, to 101° F. at night followed by a marked night sweat. Chest x-ray was

TABLE I. MATERNAL BLOOD COUNTS

	9/5	10/6	11/6	12/4	12/28	1/28	3/10	3/22	3/26	3/29	3/31	4/2	4/9	4/14	4/21	4/28	5/5	5/26	6/26
R.B.C.	3.87	3.32	3.21	3.44	3.08	2.89	4.10	3.92	3.78		3.87	3.67		3.87	4.01	4.06	4.01	4.13	4.20
Hgb. (%)	70	62	61	60	59	53	71	72	66		67	67		68	72	72	73	75	76
W.B.C.							9,050	8,850	12,700		11,800	15,500		9,450	8,850	9,450	6,550	7,550	8,600
Segs.							70	71	54		33	20		31	36	36	44	48	47
Band.										DELIVERY		2							
Lymph.							25	26	40		60	70		63	60	59	51	47	52
Eos.							3		1			1							
Basos.							2					1		1		1	1		
Monos.								3	5		7	6		5	4	4	4	5	1
Heterophile								Neg.				Neg.	Pos.						

TABLE II. INFANT BLOOD COUNTS

	4/6	5/1	5/4	5/12	5/16	5/19	5/26	6/2	6/9	6/16	6/26	7/3
R.B.C.	4.31	1.92		3.56	3.00	3.09	2.75	3.22	3.15	2.98	3.32	3.86
Hgb. (%)	85	30		60	51	52	47	53	53	49	57	63
W.B.C.	10,600	6,300		6,300	6,500	7,200	7,950	7,500	8,750	6,200	7,050	6,250
Segs.	54	20		19	18	19	23	25	15	20	24	26
Lymph.	39	71		77	79	75	73	71	81	77	72	70
Monos.	6	7		4	3	4	3	3	4	2	4	3
Eos.	1	2	TRANSFUSION	0	0	2	1	1	0	1	0	1

negative on March 22. Physical examination continued negative; the fetus enlarging. Red blood count at this time was 3,920,000; hemoglobin 72 per cent; white blood count 8,850, with segmented cells 71 per cent; lymphocytes 26 per cent; monocytes 3 per cent. Agglutination reactions for typhoid, typhus, and melitensus were negative. Heterophile agglutination was negative. On March 26, a differential smear revealed a rather marked change in the poly-lymph distribution, 54 per cent and 40 per cent, respectively, so that infectious mononucleosis was suspected.

On March 28, in view of the extreme debility of the patient, continuation of fever, absence of a positive diagnosis, and concern for the fetus, it was determined that labor should be initiated by rupture of the membranes. This was done at 8 P.M. Labor began at 10 P.M., and at 1:30 A.M. on March 29, a 4-pound 13-ounce female infant was delivered in the left occipitoanterior position with outlet forceps. The child cried spontaneously.

In all, the patient was in hard labor for three hours, normally delivered, with a normal third stage. On March 31, 1945, four days post partum, the diagnosis was tentatively established as infectious mononucleosis, the blood count revealing a continuing change in the normal white cell proportion:

Red blood cells, 3,870,000	White blood cells, 18,750
Hemoglobin, 67 per cent	Segmented cells, 63 per cent
	Lymphocytes, 60.5 per cent
	Monocytes, 6.5 per cent

However, on this same date the heterophile antibody reaction, as well as the typhus, typhoid, and melitensus, remained negative.

Postpartum course was normal except for a continued evening temperature rise of 99.6° or 100° F. Debility was marked for the first three days but then began to disappear rapidly. Appetite developed for the first time in weeks. On April 2 the white cell disproportion had become even more marked: polys 20.5 per cent, and lymphocytes 70 per cent. On April 9 the diagnosis was finally established by positive heterophile reaction, in a dilution of 1:128. The subsequent course has been a general progressive improvement in the patient, as well as a gradual rearrangement of the white cells to the normal pattern (Table I).

As a matter of interest, a complete blood count was done on the infant on the seventh postpartum day. It revealed:

Red blood cells, 4,310,000	White blood cells, 10,600
Hemoglobin, 85 per cent	Segmented cells, 54 per cent
Occasional nucleated red cell	Lymphocytes, 39 per cent
	Monocytes, 6 per cent
	Eosinophiles, 1 per cent

The child, weighing 4 pounds, 13 ounces, at birth, was considered premature. She was placed on a weak evaporated milk formula, given subcutaneous fluids twice daily, and kept warm. Progress was normal and weight was 6 pounds, 3 ounces, at the first month. At this time and for several days prior, it was noticed that although the child cried and ate well there was a progressive pallor and waxiness. A surprising red count was found on May 1, 1945:

Red blood cells, 1,920,000	White blood cells, 6,300
Hemoglobin, 30 per cent	Segmented cells, 20 per cent
	Lymphocytes, 71 per cent
	Monocytes, 7 per cent
	Eosinophiles, 2 per cent

In spite of the fact that the child was then a month old, concern was felt regarding the Rh factor. The mother and father proved to be Rh positive and the infant Rh negative. On May 3 the child was transfused with 150 c.c. of Rh-negative blood, given in the bone marrow of both tibiae. There was an immediate improvement in the count and general appearance. Red blood count was 3,560,000, with 60 per cent hemoglobin on May 12. However, four days

later the count had dropped to 3,000,000 with 51 per cent hemoglobin. Physical examination of the infant was normal. She was gaining well, cried lustily, and nursed well. The spleen was not palpable. It was thought advisable to start 2 grains of ferrous sulfate daily by mouth.

The count remained about the same until May 26, at which time it dropped to 2,750,000, with 47 per cent hemoglobin. During this time the white blood cells remained within limits of 6,000 to 8,000 with about a 70 per cent lymphocyte and a 20 per cent segmented cell proportion. This was considered to be within normal limits for an infant. At this time, the infant began to have a dietary upset, thought possibly to be due to forcing iron by mouth, so that a change was made to intramuscular injection of iron cacodylate, ¼ grain every second day, and, in addition, 0.33 c.c. reticulogen every third day. Under this management the count continued to remain at about 3,000,000 with 50 to 53 per cent hemoglobin until June 16. At that time the spleen became palpable about 1 fingerbreadth below the left costal border. The dietary upset had disappeared with the discontinuation of iron by mouth and the child appeared to be doing well, weighing 9 pounds, 2 ounces (2½ months old). Since we seemed to be getting nowhere with rather large amounts of iron and liver extract, it was decided that all medication should be stopped. Strangely enough, the red blood count rose to 3,860,000 with 60 per cent hemoglobin within two weeks, and splenic enlargement disappeared. At three months the child weighed 10 pounds, 12 ounces, and concern for the anemia was dropped.

In retrospect, the case has been of considerable interest from several standpoints. Symptoms and findings of mononucleosis in the mother were somewhat different from the usual picture. We were particularly impressed with the extreme debility and mental depression, in a usually happy and vivacious personality. There was an absence of previous throat infection and no glandular enlargement. The rather high evening temperatures and particularly the night sweats complicated our consideration of the problem.

Obviously, in so far as anemia in the child is concerned, no conclusions can be reached. It appears that the Rh factor was not important. It could well have been an iron deficiency anemia, since the mother had had no iron for three months and had eaten very little for five weeks prior to the delivery. Whether or not mononucleosis in the mother was influential in the child's anemia remains to be proved.

I wish to acknowledge the assistance of Lt. Helen R. Cash, WAVE technician, whose accurate laboratory work made this article possible.

USE OF CURARE TO RELIEVE DYSMENORRHEA

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THIS clinical report is based on the use of curare* by injections on 73 occasions to 49 women, who were suffering from dysmenorrhea believed to be of primary type.

The observation that curare might be of assistance in the treatment of dysmenorrhea came about in the following manner: The literature on curare contains the report of Bennett and Cash[1] on the use of a very small dose of curare as a diagnostic test for myasthenia gravis. The test is based on the action of curare, interruption of the nerve impulse at the myoneural junction, causing brief weakness of voluntary muscles resembling the clinical picture of myasthenia gravis. The injection of one-tenth of the physiologic dose of curare will so exaggerate the weakness in a patient with myasthenia gravis as to confirm the diagnosis.

In December, 1943, I applied this test in the case of a young woman suspected of having myasthenia gravis. Prostigmine methylsulfate and atropine were at hand to terminate the added muscle weakness in case the small dose of curare should cause any severe reaction.

Intravenous injection of 50 units of purified curare caused transient lid droop and double vision but no embarrassment of respiration. An additional 50 units revealed no general muscular paralysis, so I felt that myasthenia gravis was ruled out. In a few minutes the patient arose stating, "You can use that stuff on me again, my cramps are gone!"

The possibility that minute doses of curare would influence menstrual cramps was then considered.

Shortly after this a nurse asked for help for severe menstrual pain. I administered 70 units of intocostrin in one dose, intravenously. She experienced immediate relief, returned to duty and had no return of discomfort.

After repeating the successful experiment on the nurse and the original patient, I reported the facts to Dr. Stuart Cullen. Dr. Cullen[2] had reported a large series of cases of the successful use of curare to obtain muscular relaxation in anesthetized patients without producing deep anesthesia. Dr. Cullen was intrigued by my observations because curare is believed to have no action on involuntary musculature. We agreed that we would test the effect of curare on dysmenorrhea further. He suggested to Dr. May Danielson, then a member of his anesthesia staff, that she treat University Hospital personnel whenever the occasion arose and report the results.

Dr. Cullen and Dr. Danielson have kindly given me their data for publication with my own. The Cedar Rapids series comprises the treatment of 23 women in 34 menstrual periods, and the Iowa City series, 26 women in 39 menses.

Our results were about the same. Good results were obtained in 50 per cent of the cases. By good results I mean that the patients were able to return to work immediately or within twenty to thirty minutes and to continue at their normal activities with little or no discomfort. Another group have temporary or partial relief of pain so that results are only fair. In one third of the cases there was no relief of disability or such short relief as to make the use of curare impractical.

The necessity for parenteral administration of curare limits its usefulness. Within one minute after intravenous injection of curare the patient observes heaviness of the eye-

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Two purified preparations of curare were used in these two series: Intocostrin (Squibb) and d-tubocurarine chloride (Squibb).

*The materials used in this study were furnished by E. R. Squibb & Sons.

lids and often diplopia, or fuzzy vision. These effects pass in five to ten minutes. The relief experienced is immediate, coming on within two to fifteen minutes after the intravenous injection of 50 to 100 mg. of curare. A second dose of 50 mg. has been given in some instances, several hours after the initial dose. The disabilities relieved comprise cramps, nausea, backache, dizziness, and a feeling of tension.

One patient experienced dizziness lasting a half hour after the injection and fainted when she got to her feet. She was of very slight build and had received 100 mg. as an initial dose. Another time I would give such a patient a smaller initial dose.

The frequency of occurrence of dysmenorrhea has been the subject of many investigations. Any subjective complaint cannot be mathematically evaluated. Novak[3] quotes M. Hodge as an authority that 5.3 per cent of 974 apparently healthy girls had such severe dysmenorrhea as to prompt rest in bed. Winther[4] found 20.6 per cent of 7,379 University of Minnesota women students had discomfort sufficient to necessitate going to bed.

Dysmenorrhea, including menstrual pelvic pains, headache, leg ache, nausea and vomiting, and tension must represent a considerable loss of time in industry. Prompt and safe therapy which contributes to the relief of suffering and lessens hours lost from normal occupation is of importance.

It is interesting to speculate on the modus operandi of the relief of menstrual pain experienced with the injection of curare. The drug may improve the circulation to the uterine muscles by its relaxing action on all skeletal musculature. Bickers[5] believes the pain of dysmenorrhea is comparable with that of angina pectoris and other painful muscular contractions caused by insufficient oxygenation of the contracting muscles.

With one patient being investigated between menses for sterility by hysterogram when cramping was severe after the filling of the uterus with iodized oil, a roentgenogram was made, then 100 units of curare were injected intravenously. Within two minutes of the injection, pain was less, and a second film was taken at the same distance and angle. The two films superimposed almost exactly. Probably the relief of pain was owing to the escape of the iodized oil through the open ends of the tubes and not to any relaxation of the uterus.

The need of an intravenous or intramuscular injection which may have to be repeated after four hours is the chief drawback to the convenient use of curare for the relief of dysmenorrhea. Small doses are harmless unless the patient should have myasthenia gravis. In this event the effect of the curare would exaggerate the muscular weakness and might temporarily embarrass respiration. This could be offset at once by a dose of prostigmine.

Curare does not upset glandular function as do so many of the endocrine preparations used for the treatment of dysmenorrhea. Extracts of curare are inexpensive. Another advantage of curare is that it acts instantly. The various aspirin compounds so extensively used to cover up menstrual pain cause nausea, sweating, and weakness in many instances. Curare does not have these drawbacks.

Furthermore, curare is not habit forming as are opiates, too often administered as a last resort. The repeated use of curare has appeared to be followed by less severe pain at subsequent periods, doubtless a psychological effect.

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EARLY CLINICAL AND ROENTGENOLOGIC DIAGNOSIS OF ANENCEPHALY

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THE importance of early diagnosis in fetal monstrosities cannot be too greatly stressed, as it precludes the possibility of unwittingly allowing the patient thus burdened to progress to term. To the present time, however, review of reported cases of anencephaly, considered the most common type of monstrosity, shows that those diagnosed before delivery and definitely confirmed by x-ray are very few in number. This is true even in instances where prenatal care was instituted as early as the second or third month of pregnancy. It was found, too, that in those diagnosed, suspicion of defect was generally not initiated until about the seventh month of gestation, at which time there usually was a rapid uterine enlargement because of hydramnios.

Associated with this increase in amniotic fluid very frequently is an indistinct or absent fetal heart tone; however, this diagnostic feature is thought to be due also, in part, to the fact that "the cardiac muscle, although physiologically formed and sufficiently nourished, is lacking in innervation for its function because the cerebral and even spinal centers may not be developed" (Gigli).

Accompanying the uncertain heart tones may be a subjective and palpatory lack of fetal movement. When elicited, it is of the exaggerated spasmodic or convulsive type and may partially account for complaints of abdominal pain by the patient, which, it seems, are present more often than in the normally pregnant woman.

Also, with obscurity of outline of the fetal skeleton or faulty outline of the presenting part, the possibility of abnormality must be entertained.

With these facts before us, we submit the following case:

L. E., a 27-year-old, unmarried, white girl presented herself for examination complaining of occasional dull abdominal pain of recent origin. Inspection and palpation of the part on April 3, 1945, revealed a symmetrical, tense, cystic mass filling the lower abdomen and extending to the umbilicus.

Although history of exposure to pregnancy was elicited, and last menstrual period admittedly was early in October, 1944, with abdominal palpation no ballottement was noted and no fetal parts could be definitely outlined. No fetal heart tones nor uterine souffle could be heard, and no fetal movements were felt. Subjective fetal movement had been denied to the time of initial palpation; infrequent spasmodic movements were noted thereafter. Breasts were tense with slightly enlarged areolae and prominent Montgomery tubercles. Pelvic examination showed external genitals negative, outlet marital, marked congestion of vaginal and cervical mucous membranes to actual purplish discoloration. Cervix was normal in size and position, but presented a softened tip. Fundus was felt to be enlarged and soft. Adnexa were negative. The remainder of the physical examination was also negative.

Since the presumptive signs of pregnancy were so clearly defined, but presence of a normal fetus was questionable, it was felt that x-ray was indicated to confirm the probability of a fetal abnormality. Diagnosis of an anencephalic monster was established by this method, as roentgenogram on April 4, 1945, showed a single fetus of approximately four to four and one-half months development, whose skull formation was replaced by two small ossified knobs. The uterine shadow was well outlined and was larger than expected with a fetus of this size corroborating the impression of hydramnios. Repeat films several days later verified the diagnosis of anencephaly with hydramnios and showed surprising increase in the uterine size.

The patient was referred for hospitalization on April 10, 1945, and the following summary received:

Prenatal course continued uneventful except for a gradual increase over normal in amniotic fluid; no fetal heart tones were heard although occasional movement was still noted by the patient. On April 22, when the uterus had increased to the size of a seventh month pregnancy, fetal movements ceased.

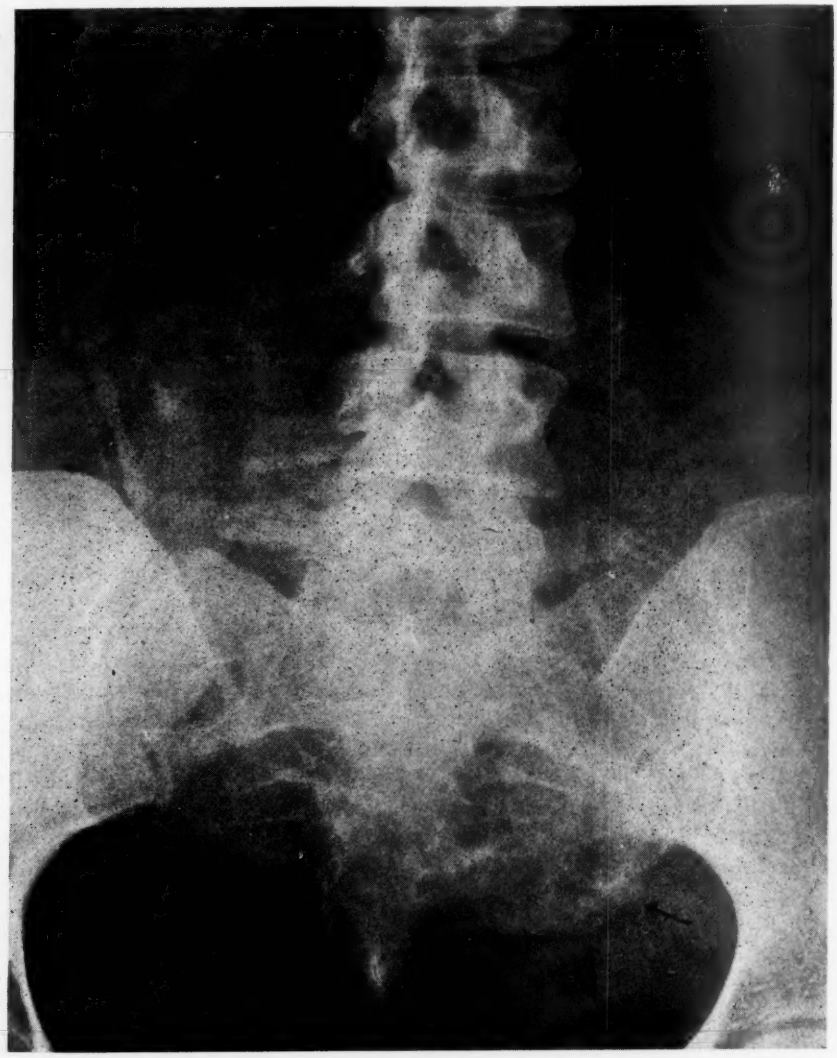

Fig. 1.—Arrows point to the two calcareous knobs which replace the normal skull formation.

On April 25, membranes were ruptured and approximately 700 c.c. of fluid escaped at the time. Drainage of fluid continued the following day with a few uterine contractions. On April 27, the patient had moderately severe uterine contractions and her previously normal temperature rose to 101.3° F. with attendant rapid pulse of 128 per minute. She appeared ill and was started on penicillin, 30,000 units every two hours intramuscularly. That afternoon vaginal examination revealed cervical dilatation of 1 to 2 cm. and during examination the left arm prolapsed. Under sodium pentothal anesthesia, the cervix was further dilated to 3 to 4 cm. and the other arm prolapsed during this procedure. After dilatation, the macerated anencephalic fetus was extracted with some difficulty. Placenta and membranes were expressed complete. Immediate condition of the patient was good. Two days later penicillin was discontinued and her convalescence progressed satisfactorily.

Gross pathologic examination of the specimen revealed a fetus with a crown rump length of fifteen centimeters, about four and one-half months gestation, the cord and placenta at-

tached. Outstanding features of the fetus were replacement of the calvarium by a sac of edematous fluid which had been ruptured, and ascites which distended the abdominal wall to a thin membrane. The eyes were bulging and the forehead receded. The tongue and lower jaw were torn in delivery and revealed a fused hard palate. The spinal column was not fused. External genitals were of the female type. The brain was represented only by dilated nervous tissue over the expanded ventricles. The bones of the calvarium were missing and the skull was formed by the fused sphenoids which protruded backward from the spine. The spinal cord was exposed and the neural arches of the vertebrae extended laterally instead of posteriorly and were flattened over the center of the vertebral column. On sectioning, the liver was flabby and torn. The intestinal tract had a gangrenous, infected appearance. Heart was normal in appearance. Because of maceration throughout, no sections were made.

TABLE I

AUTHOR	GRAVIDA	SIGNS OR SYMPTOMS SUGGESTING X-RAY	FETAL HEART	DURATION OF PREGNANCY (WEEKS)
Case, J. T.	iv	Hydramnios; no fetal movements	No	28
Case & Cooper	iv	Hydramnios	Yes	32
	iv	Hydramnios	?	32
	iv	Hydramnios; prenatal care from 3 months	Yes	28
Tracy, F. E.	i	Hydramnios	Faint	32
	i	Hydramnios; prenatal care from 2 months	No	30
Jennings, C. H.	iii	4 wk. overdue; abnormal presenting part; prenatal care from 3 months	Until 48 hrs. before delivery	43
Harris, A. T.	vi	Hydramnios	?	40
Doub, H. P.	i	Hydramnios	Yes	30
	i	Hydramnios	?	36
Maier, R. J.	i	3 weeks overdue	Yes	43
	i	Hydramnios	No	30
Spangler, D.	?	Hydramnios	?	36
	iii	Toxemia	No	34
Winn, et al.	i	Toxemia; hydramnios patient a diabetic	No	26
	v	Hydramnios	No	28
	iv	Hydramnios	No	40
Lloyd	?	Question of pregnancy; no subjective fetal movement	?	33

Discussion

Several salient features of the above case demand attention, first and most important of which we consider to be the early diagnosis. According to menstrual history at the time of initial examination, the pregnancy should have been about 25 weeks in progress. However, palpation found the upper uterine boundary not to exceed the level of the umbilicus. It is recognized that an anencephaly fetal growth is stunted, particularly in the early months of pregnancy. Body measurements of various parts are less than in the normal fetus for the same period of development. On this basis we shall assume that the dates of history approximate the correct, even though the gross pathologic report describes the fetus as of four and one-half to five months' development.

Recognizing the fact that the fetal skeleton in its entirety cannot be well visualized by roentgen ray until about the eighteenth week, it is felt that this represents one of the earliest cases diagnosed clinically and confirmed by x-ray. Radiographic absence of a skull shadow alone was not used as a criterion for diagnosis as that is of no great significance; a rapid fetal movement will obliterate that shadow, particularly if the exposure is over one second. However, the replacement of the skull shadow by two small round ossified knobs (sphenoids)

is quite characteristic of the anencephalic development. In an older fetus, even the facial bones may be distinctly seen crowned by the small knobs described.

Another feature of this case to be mentioned was the presence of an almost complete spina bifida which in some degree usually accompanies anencephaly. Occasionally this deformity can be diagnosed from the abdominal film, particularly if the defect is very large and the rib ends are considerably separated from the vertebral bodies.

Initial palpation of the uterus revealed no appreciable hydramnios. However, in the short interval of four days between x-ray films, the fluid had already increased and was clearly illustrated by comparison of the uterine outline in those films. This indicates the rapidity with which amniotic fluid is secreted in abnormal pregnancies.

Since 1916, at which time diagnosis of fetal monstrosity was first substantiated by x-ray, approximately only eighteen cases have been reported with confirmation by x-ray. Résumé of these cases is charted in Table I.

Of special interest on the above chart are the three cases which had prenatal care instituted in the second or third month. Also to be noted are the two instances in which the patients progressed three to four weeks beyond the expected date of confinement.

Parity of the patient seemed not to influence the occurrence of the monstrosity, as it was well divided apparently between primiparae and multiparae. Although not specifically shown here, the maternal age group was also deemed nonrelated to incidence. Hydramnios was the predominant cause for suspecting abnormality and suggested the wisdom of check x-ray. As has been mentioned, hydramnios was usually around seven to eight months in appearing. The above chart also concurs with the fact that the fetal heart tones are frequently not heard, or, if present, are likely to be weak.

It is felt that discussion of the case would not be complete without mention of the fact that details of delivery were not accorded the patient to circumvent the possibility of exciting a psychosis with future pregnancies.

Summary

A case of anencephaly has been reported in which clinical and roentgenologic diagnosis was made relatively early in fetal life. With modern technique, a simple anterior-posterior film of the pelvis early in pregnancy is fraught with absolutely no danger to the mother or fetus. Therefore, in cases of questionable diagnosis this facility for clarifying it should be readily used. It is felt that diagnosis of abnormalities of this type with subsequent therapeutic abortion is of obstetric as well as psychological value.

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ARGENTAFFIN CARCINOMA (CARCINOID TUMOR) ARISING IN AN OVARIAN DERMOID CYST*

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IN 1939, Stewart, Willis, and de Saram[1] observed for the first time the occurrence of carcinoid tumors arising in connection with ovarian dermoid cysts. In their first case, because of inadequate material for study, these authors were unable to find the intestinal tissue of origin, but, in their second example, they clearly demonstrated that the tumor arose from epithelium of the type found lining the normal ileum. Of noteworthy interest was the fact that, although this intestinal tissue did not form a complete segment of gut, strands of "muscularis" were present, and these strands were markedly hypertrophied in zones which were infiltrated by tumor. This phenomenon of myohypertrophy had been previously described in cases of carcinoid tumor involving different segments of gastrointestinal tract, but it had always been ascribed to the effects of intestinal obstruction and not to any direct action on the part of the tumor cells.

In recording the third case of this pathologic curiosity Gabrilove[2] was able to identify a diminutive segment of gastrointestinal tract including a portion which appeared histologically to be lined by gastric mucosa. In this mucosa numerous nodules of carcinoid tumor were found. His case was the only one of its kind from the standpoint of a "dermoid" origin, and the fourteenth recorded instance of carcinoid tumor arising in gastric mucosa.

While studying a large series of dermoid cysts we encountered, more or less accidentally, a very small nodule of argentaffin carcinoma (carcinoid tumor) in an ovarian cyst. The following is a brief report of our case.

Report of Case

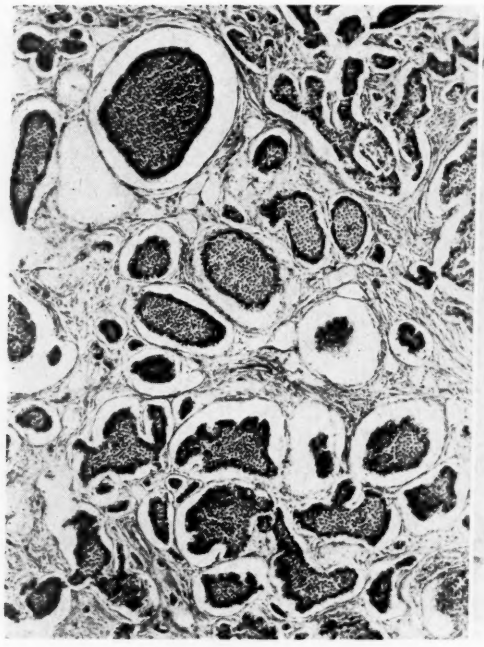
A white woman, 59 years of age, came to the Mayo Clinic on May 2, 1938, complaining of constant suprapubic pain of eight days' duration. For one year prior to this episode she had had a dull intermittent aching pain in the right lower portion of the abdomen. For a similar period she had suffered from mild nocturia. Her menstrual history had been normal and the menopause, which she had experienced at the age of 53 years, had been uneventful. She had had one child.

Positive physical findings were limited for the most part to the examination of the pelvis, which revealed bilateral masses the size of a grapefruit, which were believed to be cystic, and considered as being probably ovarian in origin.

At operation, through a low midline abdominal incision, bilateral ovarian dermoid cysts were found. The uterus contained multiple small fibromyomas. Hysterectomy with bilateral salpingo-oophorectomy and appendectomy were performed.

From the standpoint of our report, the ovarian "dermoids" furnished the main points of interest. Each was approximately 8 cm. in diameter, unilocular, and almost completely cystic. The content of sebaceous material, hair, and so forth, was that which one usually expects, and the small "dermoid processes" were not remarkable grossly. Blocks of tissue

*In deference to common usage, the term "dermoid cyst" is herein used instead of the more accurate designation "cystic teratoma."



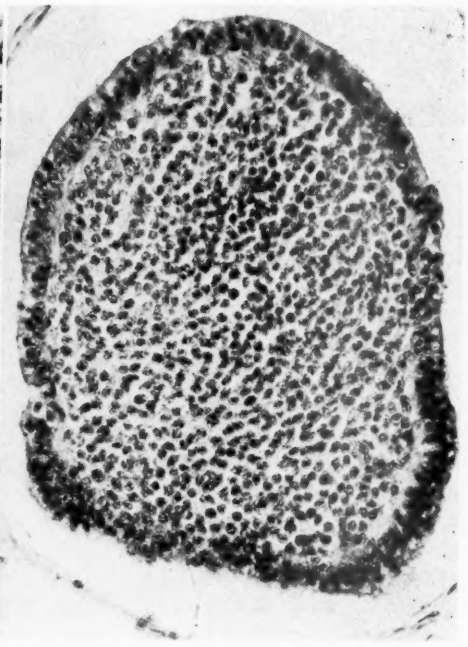


Fig. 1.—Details of a cellular island of tumor tissue illustrating the phenomenon of peripheral palisading of cells (hematoxylin and eosin).

Fig. 2.—Argentaffin carcinoma (carcinoid tumor) occurring within a dermoid cyst. The cells are small and hyperchromatic and are disposed in islands and strands which appear separated by tissue clefts from the surrounding stroma (hematoxylin and eosin).

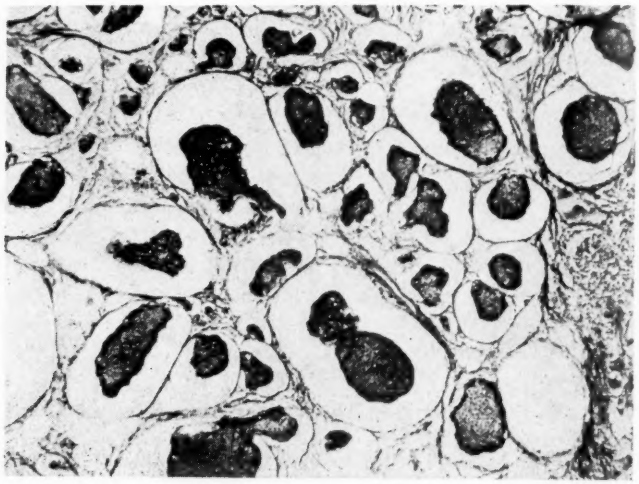


Fig. 3.—The argentaffin character of the cells is seen with a blackening of the cytoplasmic granules (silver impregnation method).

sectioned and stained in the usual way revealed squamous epithelium, eccrine and apocrine sweat glands, sebaceous glands, and hair follicles. In addition, isolated patches of brain tissue, bone, smooth muscle, adipose connective tissue, bronchial epithelium, and peribronchial mucous glands were encountered. In one of the blocks routinely selected from the left ovarian tumor a microscopic-sized portion disclosed, with hematoxylin and eosin preparations, an appearance which at once suggested the diagnosis of carcinoid tumor (Fig. 1). The cells were small, prismatic in shape, dark-staining and granular, and were arranged in islands and strands which exhibited a degree of palisading of the peripheral layers (Fig. 2). Comparing the appearance of the tumor with that of a large group of ileal carcinoids (reported elsewhere by one of us [Dockerty] and Ashburn[3]) it was evident that our diagnostic impression was a certainty. Preparations on other blocks, using silver impregnation methods, confirmed our findings, the cytoplasm of the tumor cells showing numerous argentaffin granulations (Fig. 3). Search was then carried out on remaining portions of the block and on adjacent tissue subsequently taken from the original tumor in an effort to establish the identity of the gastrointestinal tissue of origin. Our attempts were unsuccessful and, accordingly, we were left to assume that the neoplastic process had begun in a small group of cells rather than in a macroscopic segment of intestine as found by Gabrilove. Since we have not found any reports other than the afore-mentioned, we are accordingly submitting our case as representing the fourth example of argentaffin carcinoma (carcinoid) occurring within a dermoid cyst.

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RECURRENT PLACENTA PREVIA AND THE SIGNIFICANCE OF PLACENTOGRAPHY AS A DIAGNOSTIC CRITERION

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WITH an incidence of placenta previa at the Boston Lying-In Hospital of 1:92,[1] one would expect a reasonable number of such patients to repeat their experiences. However, a search of case histories at this hospital shows that this complication recurred only in two patients since 1925. A review of the literature reveals only ten cases of recurrent placenta previa in successive pregnancies,[2, 7] and one case in nonsuccessive pregnancies.[8] The scarcity of cited instances of recurrent placenta previas cannot be ascribed to the failure of obstetricians to report these cases but, more likely, to the fact that placenta previa recurs only rarely, as demonstrated in our statistics. Fried and Torpin[7] report the most recent case of recurrent placenta previa in successive pregnancies since 1931. Vaginal examinations did not establish conclusive evidence of placenta previa in either pregnancy. Concerning the patient's first pregnancy, they say: "No placental tissue was felt at the os, which was found to be dilated 3 cm. and slightly effaced." Vaginal examination in the subsequent pregnancy "failed to reveal placental tissue near the cervical os, which was found to be dilated 2 cm. and uneffaced." On each occasion the patient was delivered uneventfully via the pelvic route.

It is the purpose of this report to present two cases of recurrent placenta previa, one, in nonconsecutive pregnancies, and the other, in consecutive pregnancies.

CASE 1.—Mrs. C., a 25-year-old primipara, due March 2, 1940. She was admitted to the hospital on Feb. 19, 1940, for evaluation of painless vaginal bleeding. Twelve hours prior to admission she passed about three teaspoonfuls of bright red blood with several small clots. Palpation of the abdomen showed the vertex to be floating high over the inlet. Cystograms and soft tissue films showed evidence of placenta previa, because the placenta was visualized low on the posterior uterine wall. These findings were immediately corroborated by vaginal examination, performed in an operating room prepared for an immediate abdominal section. Placental tissue was palpated 1 cm. from the internal os on the posterior uterine wall, extending to the left lateral wall. Since moderately brisk bleeding resulted from this examination, a rapid classical cesarean section was performed, and an active 7-pound, 9-ounce male infant was delivered. At operation, the placenta was readily identified on the left posterior aspect of the lower uterine segment, extending within 1 cm. of the internal os. Diagnosis: marginal placenta previa.

In her second pregnancy, Mrs. C., due Feb. 17, 1941, was admitted to the hospital on Jan. 29, 1941, for evaluation of painless vaginal bleeding (approximately 8 c.c.). Placentography revealed the placenta again attached to the posterior uterine wall with the greatest thickness at the equator of the uterus. The vertex was floating over the inlet. Since there was no vaginal bleeding after five days of hospitalization, she was discharged. It was decided that she should be admitted on the due date to await pelvic delivery. On February 26, the patient was delivered uneventfully, by low forceps, of an

8-pound, 14-ounce female infant. Exploration of the previous section scar showed it to be intact.

In her third pregnancy, Mrs. C was due Nov. 25, 1943. Abdominal palpation on October 13 revealed the vertex floating high over the inlet. Since there was a question of hydrocephalus, a lateral film of the uterus was taken. The vertex was found to be normal, but the placenta was visualized low on the posterior wall, consistent with the diagnosis of partial or complete placenta previa. A flat plate of the abdomen showed the fetal head displaced toward the right iliac fossa. It was evident that the patient had a greater degree of placenta previa in this pregnancy than in her primiparous one. Therefore, an elective repeat cesarean section was scheduled one week from term. The patient was admitted to the hospital on Nov. 18, 1943. A severe upper respiratory infection necessitated postponement of the operation. However, 36 hours after admission, the patient passed several small dark clots. Therefore, on Nov. 20, 1943, the patient was delivered by means of a Krönig cesarean section of an active 8-pound, 11-ounce male infant. The placenta was found low on the posterior uterine wall, completely covering the internal os. Diagnosis: complete placenta previa.

CASE 2.—Mrs. M. R., was a 40-year-old para vii, due Oct. 16, 1942. The past obstetric history revealed that the patient had been delivered five times normally and once by breech extraction. The fifth pregnancy resulted in a stillborn infant because of premature separation of a normally implanted placenta.

The patient was admitted to the hospital with her seventh pregnancy at 12:30 A.M. on Sept. 26, 1942, because of bright red vaginal bleeding (approximately 6 to 8 c.c.). Previously there had been a small amount of vaginal bleeding at the third and sixth months. The blood pressure on admission was 124/76, the pulse rate 80, and the patient's condition was good. Examination of the abdomen revealed the vertex floating over the inlet. The infant lay in the right occipitoposterior position. The fetal heart was heard in the right lower quadrant at the rate of 132 beats per minute. Soft tissue films, taken shortly after admission, showed the placenta to be attached low on the anterior uterine wall, consistent with a marginal placenta previa. In view of these findings, immediate vaginal examination was made under "double set-up" precautions. The cervix was soft, not effaced, and dilated 3 cm. The placenta was palpated on the anterior wall of the lower segment and extended within 2 cm. of the internal os. Since the patient began to bleed briskly, a classical cesarean section was performed immediately. An active 6-pound, 7-ounce female infant was extracted by the vertex. The post-operative course was uneventful. Diagnosis: marginal placenta previa.

The patient, as a para viii, registered for prenatal care on Nov. 27, 1943. The expected date of confinement was Feb. 16, 1944. However, on Feb. 6, 1944, she was admitted to the hospital because of painless vaginal bleeding (8 to 12 c.c.) which began one and one-half hours prior to admission. The blood pressure was 128/66, the pulse rate, 96. Abdominal palpation revealed the vertex to be floating high above the inlet. The infant was in the left occipitoposterior position with the fetal heart rate 144, located in the left lower quadrant. Soft tissue films, taken shortly after admission, showed the placenta to be implanted extremely low on the anterior uterine wall. These findings were indicative of a complete placenta previa. Therefore, with the operating room in readiness for an immediate section, a sterile vaginal examination was made. Palpated placental tissue, covering the internal os, confirmed the diagnosis of complete previa. Accordingly, a classical cesarean section was performed. An active 7-pound, 3-ounce male infant was delivered by the vertex. At operation, the placenta was found covering completely the internal os. Diagnosis: complete placenta previa.

Comment

Recurrent placenta previa as an entity per se is an uncommon obstetric complication as shown by the scarcity of cases observed in our clinic and the relatively few cases reported in the literature. This phenomenon is difficult to explain. Since placenta previa is chiefly a multiparous complication, multiparity, together with faulty decidua, undoubtedly is the most important etiological factor.

The reason for allowing a pelvic delivery in Case 1 with the second pregnancy may be questioned by some obstetricians. When a previous cesarean section has been done for a temporary indication, it is the policy of this clinic to allow the patient to have a test of labor under close observation. These patients are delivered by low forceps shortly after full dilatation, with immediate exploration of the uterine scar. This procedure has been pursued several hundred times without the occurrence of a single ruptured uterus. Patients who were febrile in the puerperium following the original section are never given a test of labor.

The advent of placentography invaluably facilitates an early diagnosis of placenta previa. We feel that a more accurate interpretation of soft tissue films can be made by application of the following criteria.

1. If the placenta cannot be visualized upon the anterior or posterior uterine walls, a diagnosis of complete previa should be made and confirmed by vaginal examination.

2. When the maximum thickness of the placenta is visualized at or below the equator of the uterus on the anterior uterine wall, it is very likely to be a placenta previa. The likelihood of a complete previa increases proportionately with the distance of the maximum thickness of the placenta below the equator of the uterus.

3. When the placenta is visualized low on the posterior uterine wall, displacing the presenting part three or more centimeters from the tip of the sacral promontory or from the base of the fifth lumbar vertebra, a diagnosis of placenta previa should be accepted and corroborated by vaginal examination.

Brown and Dippel[9] noted that calculation of the distance between the presenting part and the sacral promontory was a valuable aid in the diagnosis of placenta previa for the posterior wall implantations, but no figure of mensuration was given.

In this clinic, soft tissue films are taken on all patients who have experienced vaginal bleeding during the last trimester. An exception is made only in those patients suffering shock from massive vaginal hemorrhage. Often, when the placenta is visualized high in the fundus, routine vaginal examinations are deemed unnecessary. Conversely, when the placenta is perceived below the equator of the uterus or not seen at all, prompt vaginal examination, for the corroboration of the diagnosis should ensue, always in an operating room prepared for an immediate section to assure safety.

Summary

1. Recurrent placenta previa is an uncommon obstetric occurrence.

2. The history of painless vaginal bleeding in the last trimester is suggestive of placenta previa, and an early diagnosis should be made with the aid of soft tissue films.

3. The skillful application of placentography undoubtedly facilitates the diagnosis of this serious complication of pregnancy.

4. Vaginal examination, under "double set-up" precautions, and cesarean section confirmed the diagnosis of recurrent placenta previa in the cases presented above.

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VESTIBULAR ABNORMAL ANUS IN A PREGNANT WOMAN

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(From the Burnside Obstetrical Division of the Toronto General Hospital, and the Department of Obstetrics and Gynaecology, the University of Toronto)

THE vestibular abnormal anus is an anatomic phenomenon which resembles a "complete tear" of the perineum. There is present a rectovaginal spur, thick in its upper two-thirds, and becoming gradually thinner in the lower third. Control of the feces and flatus is perfect, so that whilst anatomically there is much to be desired, functionally the result is very good. In the *Revista médica municipal* of Rio de Janeiro, 1942, volume 5, page 53, De Oliveira Figeiredo reported two cases showing this interesting abnormality. In reviewing the literature he quotes Trelak, who states that the condition occurs once in every 73,000 labors. The writer recently delivered a woman who presented this abnormality.

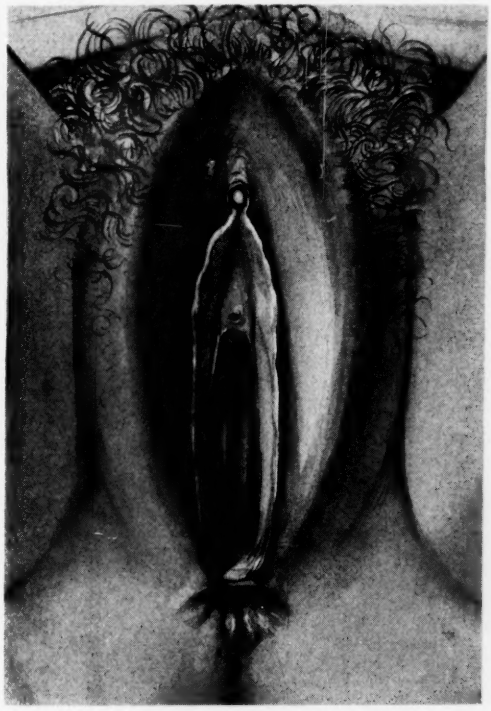

Fig. 1.

Case Report

Mrs. T., a para i, was first seen on Jan. 27, 1942. Her last menstrual period had been on November 20. The uterus was enlarged to the corresponding period of amenorrhea. Pelvic examination disclosed the following condition. There was no perineum. The labia minora were large and extended to the anal orifice where they blended with the skin around a very weak and incomplete sphincter ani muscle. The labia majora were well developed. The rectovaginal spur was very thick in its upper two-thirds. The levator ani

muscles were exceptionally well developed. The lower third of the rectovaginal septum resembled a typical "complete tear" of the perineum. The drawing (Fig. 1) depicts the phenomenon with its anatomic peculiarities. The prenatal period was normal. The labor was uneventful except for one complication—the well-developed levator ani muscle "straps" were most resistant and prevented descent of the head in the second stage. Forceps were used to complete the delivery. In order to preserve the rectovaginal septum, a wide and deep lateral episiotomy was performed. The child weighed 9 pounds, 13 ounces. The episiotomy wound was sutured immediately with chromic catgut No. 1. The total duration of labor was 48 hours. The puerperium was afebrile. Subsequent examination showed the rectovaginal septum intact, and the episiotomy wound well healed.

OPISTHOTONUS FETALIS

ALFRED J. KOBAK, M.S., M.D., CHICAGO, ILL.*

(From the Department of Obstetrics and Gynecology of the University of Illinois College of Medicine)

EXAGGERATED deflection attitude of the fetus during parturition is rare, if the paucity of such case reports in the literature is any gauge. The following case report exemplifies such a condition:

D. A., aged 20 years, para i, gravida ii, had a normal prenatal course. She gained 35 pounds despite thyroid medication and dietary restrictions. Routine abdominal examination prior to the onset of labor failed to reveal any abnormal attitude of the fetus.

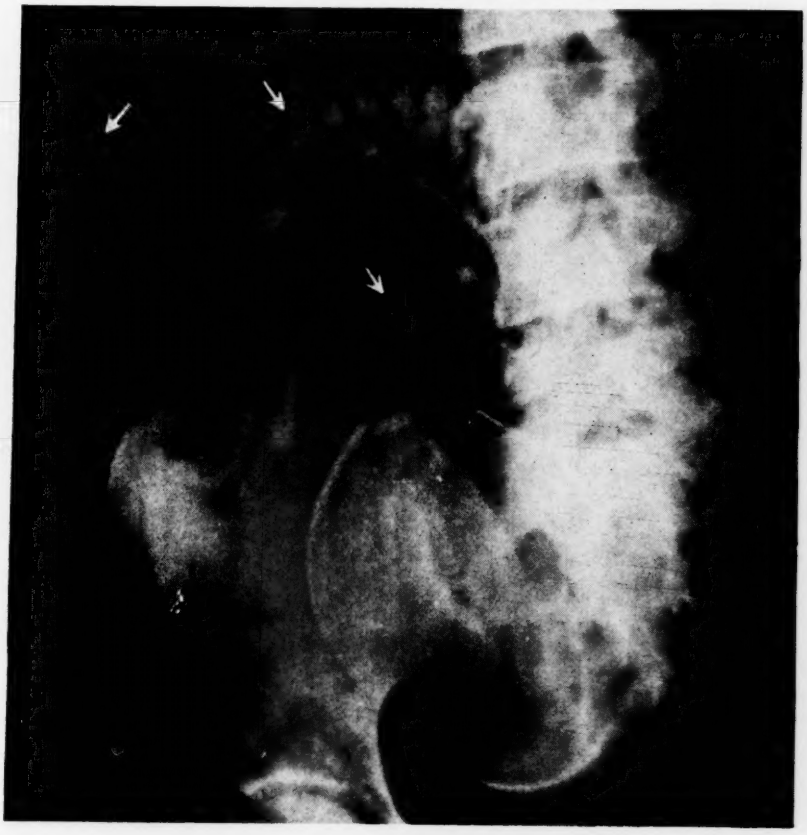

Fig. 1.

The patient was admitted to the Wesley Memorial Hospital on May 6, 1945, in labor and full term. The pains began at 10 A.M.; the first examination at the hospital revealed the presenting part to be floating. At 10 P.M. the cervical dilation was 7 cm., the membranes were intact, and the face was presenting as a mentum left transverse. However, it was diffi-

*Presented before the Chicago Gynecological Society, May 18, 1945.

cult to account for the occipital prominence and the small parts both being on the right side. Considering the possibility of some abnormality, an immediate x-ray examination was made, and the roentgenogram revealed a severe hyperextension of the fetus with both arms and legs directed to the same side as the back, the right side (Fig. 1). No skeletal anomaly was present.

A baby girl weighing 8 pounds and 4 ounces was delivered by a low cervical cesarean section at 11:45 P.M. The baby maintained a posture of extreme opisthotonus, and had difficulty in respiration. A catheter was passed into the trachea without any difficulty and no mucous was obtained upon respiration. The breathing continued as though there was some obstruction. The baby was transferred into an incubator and was supplied with oxygen. Alpha lobeline, coramine, and vitamin K were given. The prognosis was deemed to be poor. At 4 A.M. the rectal temperature was 104.2° F. The baby took liquids and soon responded favorably. The posture of the baby was still one of opisthotonus, with the arms drawn sharply back behind the arched vertebral column, bringing the scapular wings toward the midline. The care of the baby was referred to Dr. W. W. Swanson who noted that the fetus was cyanotic, but responded to oxygen. The breath sounds were harsh and dry. Breathing was through the mouth and was entirely diaphragmatic. For a while Dr. Swanson noted that the heart tones were heard best through the right side of the thorax, but later the tones were heard in the normal position. X-ray of the thorax and lumbar region showed no abnormality. The baby gradually assumed a more normal posture, but still retained the attitude of hyperextension of its torso, and the arms were drawn back dorsally, even up to its eighth day of life. The mother made an uneventful recovery and left the hospital on the eleventh day. The baby remained for further observation in the nursery, until its discharge on the fourteenth day.

This condition is rare, a similar case was reported by F. H. Falls in 1917. Here the opisthotonus of the fetus was noted with the fetus presenting transversely. Failing heart tones during labor necessitated immediate extraction. The baby never recovered from the asphyxia neonatorum. It is apparent that the fetus may not fare well either during the labor or in the neonatal period, and that there is a tendency of this posture to remain for some time following delivery. Such a newborn infant may need more than the average available oxygen to tide it over the respiratory difficulty that is present.

Reference

Falls, Frederick H.: Surg., Gynec. and Obst. 24: 65, 1917.

25 E. WASHINGTON ST.

Department of Reviews and Abstracts

Selected Abstracts

Anesthesia, Analgesia

Zecena, A., and Recinos, A.: Short Labor and Analgesia, Obst. y ginec. latino-am. **2**: 839, 1944.

Of all the anesthetic agents and methods used for the relief of labor, the authors prefer epidural anesthesia. Their technique is as follows: 40 c.c. of a 1 per cent novocain solution are injected into the epidural space. Ten to fifteen minutes later 2 to 3 units of *pituitary extract* are injected subcutaneously. By means of this combination, not only are the labor pains diminished, but also dilatation of the cervix is hastened. Sixty patients were helped by this combined procedure without any maternal or fetal accident.

J. P. GREENHILL.

Medina, J., and Daus, J.: Peridural Anesthesia in Gynecologic Surgery, An. brasil de ginec. **18**: 415, 1944.

The authors are enthusiastic about the use of peridural anesthesia, and they give complete details of 100 gynecologic operations which they performed under this form of anesthesia. These operations were both abdominal and vaginal and included hysterectomies, oophorectomies, uterine suspensions, appendectomies, plastic operations on the vagina, vaginal hysterectomies, vulvectomies, vesicovaginal fistulas, and amputation of the cervix. The results were excellent.

J. P. GREENHILL.

Torrie, Arthur M.: Spinal Anesthesia for Cesarean Section, Anesthesiology **6**: 154, 1945.

The ever present question of anesthesia in obstetrics, including cesarean section, has received unusual emphasis during the past few years. Method and agent alike have been evaluated. The author relates his experience in 120 cases of cesarean section performed under spinal anesthesia. "One shot" spinal injection is the method employed. The technique is given in detail. Advantages and disadvantages are discussed. The author believes that in addition to its well-known disadvantages, "spinal anesthesia appears to have a greater and more profound effect when used in obstetrical patients than in the nonpregnant patient." It is, therefore, most important to have a competent, well-trained anesthetist in direct charge of each case, and all necessary equipment must be readily available for combating any trouble that may arise.

HARVEY B. MATTHEWS.

Mammary Glands

Brougher, John C.: Prevention and Treatment of Postpartum Fissured Nipples With Local Applications of Vitamin A and D Ointment, West. J. Surg. **52**: 520, 1944.

Cracked or fissured nipples are a common complication of the lactating period. It is estimated that cracked nipples occur in about 20 per cent of postpartum patients. Many treatment programs have been suggested for their prevention and cure.

The author has taken advantage of the well-known, stimulating, wound effect of vitamins A and D, and employed an ointment which incorporates these two vitamins. He applied the ointment immediately after delivery to a group of 200 postpartum women, and to a second group of 200 postpartum patients he used local cleanliness without the vitamin ointment. He concluded that the incidence of fissured nipples and secondary breast abscesses was greatly reduced by the use of vitamins A and D locally.

WILLIAM BICKERS.

Sanders, John T.: Factors Influencing the Morbidity and Mortality Rates in Gynecologic Surgery, South. M. J. **38:** 209, 1945.

A report is made upon 500 consecutive operations in private practice. An accurate appraisal of the cardiovascular, respiratory, urinary, hepatic, and water balance system of the patient must be made before operation. The sedimentation time is the best guide for the time of operation on patients with pelvic infection. Obesity is one of the great hazards in pelvic surgery. The anesthesia must be chosen to fit the individual patient.

Postoperative care takes into account pain relief, prostigmin for distention, frequent changing of position, and test breathing to prevent emboli, intelligent use of the catheter to prevent distention of the bladder, decompression of the stomach by nasal tube, and parenteral fluids containing vitamins A and C.

There was a case fatality rate of 0.2 per cent in this group, as compared with a fatality rate of 1.8 per cent in a group previously reported. The more generous use of intravenous fluids, whole blood and plasma transfusions, early and more frequent use of intestinal decompression, together with better preoperative care, accounts for the diminished fatality.

WILLIAM BICKERS.

Miscellaneous

Quinet, A. A.: Vaginal Cytology in Precocious Puberty, An. brasil de ginec. 9: 102, 1944.

The author studied the vaginal cells in three cases of precocious puberty. One little girl was 3 years, 7 months old, the second was 7 years, 8 months old, and the third was 4 years and 2 months old. A special nuclear pattern was observed in the cells in two of the children. This consisted of a dark dash with linear condensation of the nuclear chromation. A comparison of these special cells, with the cytological features of the vaginal cells in women of different ages, leads the author to the conclusion that these dashes represent a peculiarity of the upper cells of the stratum spinosum.

J. P. GREENHILL.

Potter, Edith L., and Willson, J. Robert: Artificial Insemination as a Means of Preventing Erythroblastosis, J. A. M. A. **127:** 458, 1945.

The authors review the clinical and immunological findings in cases of erythroblastosis fetalis. They report three cases of Rh negative children whose older siblings died of erythroblastosis. One of these Rh negative children was in a case of twins, in which the mother was Rh negative and the father was Rh positive. The Rh positive twin died of erythroblastosis. Another case was reported in which the mother gave birth to a set of twins, both being cases of erythroblastosis. Both died, and the diagnosis was confirmed at autopsy. The mother was Rh negative and the father, Rh positive. She was successfully inseminated with Rh negative semen and delivered a normal infant that did not show any evidence of erythroblastosis. This lends further evidence to support the theory of maternal immunization to the Rh factor as a cause of erythroblastosis.

WILLIAM BERMAN.

The Newborn

Gori, R. M., and Bayona, E.: The Vaginal Contents of the Newborn: The Genital Crisis, Obst. y ginec. latino-am. 2: 532, 1944.

The authors studied the secretion of the vagina in 200 newborn babies. The changes were the same in full-term and premature babies. These are as follows: during the first 3 or 4 days, there is a preponderance of cells belonging to the upper layers of the mucosa, whereas in the second week of life, there is a gradual increase of cells from the deeper layers. Some leucocytes and Döderlein bacilli may be found on the third day of life, but they are short lived because two weeks later none can be seen.

Babies who undergo genital crisis have red blood cells in the vaginal smears. In the opinion of the authors, the genital crisis is only an accentuation of a complicated process which all newborn girls undergo, and which should be called a birth crisis.

J. P. GREENHILL.

Heyworth, N. Sanford, and Shmigelsky, Irene: Purulent Parotitis in the Newborn, J. Pediat. 26: 149, 1945.

Purulent parotitis, according to the number of reported instances, has been considered a rare occurrence in the newborn.

The authors report five infants with purulent parotitis during this period. A definite routine of treatment by administration of sulfathiazole and incision of the gland when fluctuation has occurred, resulted in the recovery of all five cases.

JAMES P. MARR.

Howard, Philip J.: Paroxysmal Tachycardia in an Infant the Fourth Day of Life. Recovery With Digitalis, J. Pediat. 26: 273, 1945.

Paroxysmal tachycardia in the newborn is unusual, and differs from the disease in older children, mainly by its characteristic of persistence until cardiac failure and sometimes death follow, unless proper treatment is given. The author reports such a case, and outlines the therapy.

JAMES P. MARR.

Litchfield, H. R.: Asphyxia Neonatorum—An Evaluation—Etiology and Treatment, J. Pediat. 26: 279, 1945.

It is now generally accepted that the respiratory function is under the control of a medullary center which is activated by the carbon dioxide of the blood. Thus, when the blood carbon dioxide reaches a critical concentration, the center is stimulated and respiratory movements result with the inhalation of oxygen and the exhalation of carbon dioxide.

In asphyxia, due to the failure of the respiratory center to respond to the normal stimulus of blood carbon dioxide, there is a progressive accumulation of this gas, with a corresponding lowering of oxygen concentration. The longer the asphyxia lasts, the more serious it becomes, since the oxygen content of the blood may fall so low.

As etiological factors, the author lists excessive sedatives during labor, the anesthesia during delivery, together with trauma from abnormal presentation or difficult operative procedures.

He discusses his objections to old and worthless procedures of resuscitation, such as "slapping, swinging, and tubbing, also mouth to mouth breathing." The author mentions the little value of the Drinker respirator, inhalator, pulmotors, and resuscitators.

His object is to recommend after delivery immediate removal by suction catheter of all mucous plugs and fluid, injection into the umbilical vein of $\frac{1}{20}$ alpha-lobeline, and after respiration has begun, to follow up with pure oxygen supplied through a face mask. This is an extremely important article, and deserves to be read in full by all obstetricians.

JAMES P. MARR.

Macklin, Madge Thurlow: The Diagnosis of Rh Incompatibility. Especially by Microscopic Appearances: Its Relation to the Syndrome Formerly Diagnosed as Erythroblastosis, J. Pediat. **25:** 533, 1944.

The author, in a most learned and comprehensive article, redefines erythroblastosis. Erythroblastosis, as originally defined, indicated the presence of large numbers of nucleated red blood cells in the fetal livers at a stage in development, when erythropoiesis should largely be absent from the liver. Erythroblastosis, so defined, was present in many conditions other than those involving incompatible Rh factors in mother and fetus, such as diabetes in the mother, anoxemia and hemorrhage in the fetus.

Hemolytic disease of the newborn, proposed by some as a more correct term than erythroblastosis, is still not specific, because hemolysis may be caused by factors other than incompatibility of the Rh factor in mother and fetus.

Rh incompatibility is suggested as the term for the disease entity caused by a reaction between Rh antigens in the fetus, and the specific antibodies in the maternal blood to combat them.

Proved Rh incompatibility can be diagnosed in the living or dead infant when different Rh factors are demonstrable in mothers and fetus, and when the antibodies against the infants' Rh positive red blood cells are found in the infants' serum.

Some of the criteria used for the diagnosis of Rh incompatibility are of value when the fetus is full term, or when the infant lives for several days. They are not of value on fetuses lost early in pregnancy. The iron test is of value in these early cases.

JAMES P. MARR.

Pregnancy, Complications, Toxemia

Lascano, J. C., and Gonzalez, Warcalde J.: Subcapsular Hemorrhage of the Liver With Peritoneal Rupture During Pregnancy, Obst. y ginec. latino-am. 2: 757, 1944.

Nontraumatic hemorrhages of the liver are rare. However, it is not unusual to find small suffusions of blood under the liver capsule or in the liver parenchyma during the second half of pregnancy, particularly in cases of eclampsia. Occasionally, these hemorrhages become large enough to cause rupture of the liver capsule, with hemorrhage into the peritoneal cavity and even death of the patient.

In the toxemias of pregnancy, the cause of such hemorrhages may be vascular fragility, avitaminosis, changes in the blood, and anaphylactic shock. The authors report two cases in the fifth and sixth months of pregnancy. The first patient died immediately after delivery, and autopsy revealed the antemortem correct diagnosis of rupture of the liver capsule with intraperitoneal hemorrhage. In the second case, an abortion had taken place and the patient complained of severe pain in the right hypochondrium with irradiation to the back. This patient also died, and autopsy showed the same findings as in the first case.

J. P. GREENHILL.

Erickson, Carl A.: Rubella Early in Pregnancy Causing Congenital Malformations of Eyes and Heart, J. Pediat. **25:** 281, 1944.

New light has been thrown on the etiological factors involved in certain congenital malformations, by three series of cases which have been reported from Australia, in which virus infections, particularly German measles (rubella), occurring early in pregnancy seem to be definitely related to the congenital defects.

The author reports 11 cases. He points out that girls should not be allowed to pass through childhood without having had rubella. The use of convalescent serum for all women who are early in pregnancy and have not had rubella should be considered. The justification for therapeutic abortion in the infected mother should deserve attention as, Swan pointed out, 100 per cent of such babies will have serious congenital malformations.

JAMES P. MARR.

Quino, N., Nölting, D. E., and Althabe, O.: The Future of Eclamptic Patients, Obst. y ginec. latino-am. **2**: 860, 1944.

An attempt was made to follow up 220 eclamptic patients, but only 19 presented themselves for a thorough study. In all of them, renal function was normal. The eye grounds were normal in all except one who showed a slight degree of vascular-sclerosis. In 11.7 per cent, chronic hypertension was present. The authors maintain that the consequences of a mild but long-lasting pre-eclampsia are far more serious than those of a short, serious pre-eclampsia or eclampsia. The important factor in the future outcome of women with chronic hypertension is the duration of the toxemia.

J. P. Greenhill.

Steiner, Melvin D.: Aseptic Antenatal Thrombophlebitis (Phlebothrombosis), New Orleans M. & S. J. **97**: 385, 1945.

Antenatal thrombophlebitis is a rare condition in contrast to puerperal thrombophlebitis. The former is apparently a noninfectious condition in contrast to the latter.

A white primipara, 36 years of age, was first seen during an uncomplicated, afebrile abortion. Several months later she became pregnant again, and soon after experienced acute pain in the muscles of the left leg. Examination revealed tenderness and redness, but no temperature. The pain and edema subsided promptly following sympathetic lumbar block. Four months later, the same pain and edema occurred in the right leg; again there was no associated febrile reaction, and the condition was controlled by lumbar sympathetic block. The patient developed pre-eclamptic toxemia, for which labor was induced and a normal child delivered. Following delivery lymphangitis and phlebitis of the left upper extremity occurred, which was attributed to chemical irritation from infusion. Throughout all of these episodes of thrombophlebitis, the laboratory examinations cast no light upon their etiology.

A fairly complete review of the literature on aseptic antenatal thrombophlebitis is presented.

William Bickers.

Fearl, Clifford L.: Cervical Pregnancy, West. J. Surg. **53**: 71, 1945.

The theory is advanced that a fertilized ovum, passing with unusual speed down the tube and through the uterus, may reach its proper stage of growth for imbedding just as it reaches the cervix. The reason why cervical pregnancy is not more common is to be found in the fact that cervical epithelium is not well adapted for nidation.

A case of a 40-year-old woman who consulted the author because of inability to pass her urine is reported. She was catheterized, with a small amount of vaginal bleeding following the catheterization. This was the first evidence of menstruation in two months, her usual menstrual cycle being one of 30 days. Examination revealed an enlarged cervix, which was found just inside the introitus and distended the entire vagina. Upon opening the thin shell of tissue, which was the cervix, a fetus, 1.5 cm. in length, together with its amniotic sac and placenta, was removed. One month after operation, the cervix was found to be of normal size and high in the vagina. The cervical canal was patulous.

William Bickers.

Dingle, Phyllis: Prophylactic Use of Pneumoperitoneum in the Puerperium of Tuberculous Patients, J. Obst. & Gynaec. Brit. Emp. **51**: 499, 1944.

Treatment in 30 cases of tuberculosis is described. The patient is secured rest, food, fresh air, and hospitalization when necessary. Pneumothorax is used when indicated. The first stage of labor is made as easy and as comfortable as possible. The second stage is shortened and the strain reduced by making an episiotomy and using obstetric forceps. Pneumoperitoneum is induced within one hour after delivery using 3,000 c.c. of air or air-oxygen mixture. The amount added is gradually reduced during one month. The mother

is on bed rest and does not breast feed her infant. The pressure in the abdominal cavity after pneumoperitoneum is 10 c.c. water. Under this regime, the survey shows that these patients have not been seriously affected by their pregnancy. Out of 30 cases, two were hopeless from the start and one retrogressed. Induction of pneumoperitoneum is advocated as a prophylactic measure in these cases.

WILLIAM BERMAN.

Erskine, John P.: A Case of Acute Hydramnios Successfully Treated By Abdominal Paracentesis, J. Obst. & Gynaec. Brit. Emp. **51**: 549, 1944.

The author reports a case of acute hydramnios in a 21-week pregnancy (twin). Seven pints of liquor were withdrawn using a lumbar puncture needle inserted through the abdominal wall. The needle was attached to rubber tubing to a suction pump on the water tap. Three weeks later the same procedure was carried out because of a recurrence. Four and one-half weeks after this 11 pints of fluid were withdrawn. Six weeks after this 11 pints of fluid were again withdrawn. The patient delivered uniovular twins at 36 weeks, one of which was stillborn. The puerperium was uneventful.

WILLIAM BERMAN.

Chesterman, Judson T.: Choledochus Cyst Complicating Pregnancy and the Puerperium, J. Obst. & Gynaec. Brit. Emp. **51**: 512, 1944.

The etiology and the pathology are discussed. Eighty per cent of the cases recorded in the literature occurred in women. The characteristic symptoms of this condition are tumor, jaundice, and pain. Treatment varies in the different cases. Marsupialization gives uniformly bad results. Anastomosis of the cyst to the duodenum has given good results. The technique of the anastomosis is described in brief. All cases, according to the author, terminate fatally unless operated upon, and anastomosis to the duodenum is a simple and satisfactory procedure.

WILLIAM BERMAN.

Necrology

SIR COMYNS BERKELEY, prominent English obstetrician, gynecologist, and author for almost half a century, well known in the United States, where he visited on several occasions, died in London, Jan. 27, 1946, at the age of 81. Knighted in 1934 for his professional attainments, Sir Comyns was a Fellow of three Royal Colleges; he was a prolific and forceful writer, the author of numerous textbooks and treatises, and the editor for twenty years of the *Journal of Obstetrics and Gynaecology of the British Empire.* His name also is intimately associated with the growth and development of the Middlesex Hospital of London, where he served from 1903 until the time of his death. The present system of midwife practice in England owes much to his devotion and encouragement. The whole life of this eminent man was absorbed by his profession, which "he pursued with undeviating energy, courage and zest until well beyond the age of normal retirement." His American colleagues may well pay a tribute to this outstanding career of a forceful and engaging figure who, moreover, followed with great interest the course and progress of this JOURNAL, and at one time had under consideration an amalgamation of our mutual interests.

Correspondence

The Combined Method in the Treatment of Cancer of the Cervix

To the Editor:

I have read with great interest in the December (1945) issue of the JOURNAL the valuable contribution of Dr. Brooke M. Anspach, entitled "A Review of the Problem of Cancer of the Cervix," and, in view of my long association with the problem, desire to comment upon certain of his statements.

Dr. Anspach presents a very lucid and complete description of the development of the treatment of cancer of the cervix from the time of Wertheim to the present day. Among his conclusions is the following sentence: "Perhaps a combination of irradiation and operation will give better results." Dr. Anspach shows in a most convincing manner why Wertheim's operation was abandoned because of the high attendant mortality. Apparently the fact escaped his attention that Schauta and his school in Vienna endeavored to overcome these objections by the substitution of the less dangerous extended radical vaginal hysterectomy. I believe that I am the only pupil of Schauta in this country, and therefore feel impelled to call attention to the fact that the results achieved by the Schauta procedure equalled those of Wertheim and Bonney with a much lower operative mortality. This was demonstrated by a report based on one thousand cases which was read before the British Congress of Obstetrics and Gynecology and published in the *Journal of Obstetrics and Gynaecology of the British Empire* (**36**: No. 2, 1929). The percentage of five-year salvage was 41.7 of the operated cases as compared with 39.2 for the Wertheim, and 39.6 for the Bonney procedure.

The mortality attending the Schauta operation was 3.85 per cent, in contrast to the 16 per cent of the others. The above were the relative salvages, while the absolute five-year cures were 21.6 per cent as compared with 18.5 per cent for Wertheim, and about 22 per cent for radiation treatment (Heyman). After we at the Schauta Clinic began to treat all of our patients by a combined method of operation and radiation, our results improved remarkably. I presented our experiences in a paper published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY (**33**: 332, 1932), in which the salvages of patients treated by the combined method were compared with those not radiated. There was an increase of relative cures from 72 to 92.8 per cent in the two-year group, from 61 to 72 per cent in the three-year group, from 52 to 61.8 per cent in the four-year group, and from 42 to 58.8 in the five-year postoperative group. The absolute percentage (five-year cure) of all patients was 32.

These figures confirm Anspach's opinion that a combination of operation and radiation gives better results than either operation or radiation alone, as suggested likewise by Lynch, Taussig, Morton, and Meigs. The latter's results in 47 cases with preoperative radiation and without mortalities are indeed remarkable and justify a surgical approach and the combined procedure. However, I have always believed that we should not be dogmatic and that it constituted an error to subject all cancer cases to one method of treatment. Our aim should be to adapt the method to the specific condition found in the individual case. With this elective method I have treated 580 patients with cervical cancer during the years from 1921 to 1938. Of these there were 322 women who were under observation from five to sixteen years. Of these 322 women, there were 127 living, in March, 1938, which means a permanent salvage of 39.4 per cent. When we compare this with the average results in the world statistics of operated cases without radiation (about 19 per cent, with a peak of 25.9 per cent by Bonney), with radiation alone (20 per cent), with a peak of 27.4 per cent in Grey Ward and Healy's figures, it seems to me evident that the combined treatment gives the patient a better chance than operation alone or radiation alone.

A short description of the extended vaginal operation, and the combination with introduction of radium at the end of the operation can be found in Pack and Livingston's excellent monograph on cancer treatment (Paul B. Hoeber, 1940).

I had the privilege of demonstrating my method in a moving picture at the meeting of the American Gynecological Society at Asheville, North Carolina, in 1938.

LUDWIG ADLER, M.D.

45 EAST 82ND STREET

Reply by Dr. Anspach

To the Editor:

I am sorry that Dr. Adler's work was overlooked. It was quite certain that some one would be forgotten at the moment. I was impressed with his reports. Unfortunately, in preparing the review my attention was focused on the abdominal operation, and the vaginal one completely slipped my mind. I am glad that Dr. Adler has made this very valuable addition to my paper.

BROOKE M. ANSPACH, M.D.

1827 SPRUCE STREET
PHILADELPHIA, PA.

Items

American Board of Obstetrics and Gynecology, Inc.

Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted at Chicago, Illinois, by the entire Board from Monday, May 6, through Saturday, May 11, 1946. The Palmer House in Chicago will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing directly to the Palmer House.

Candidates for *re-examination* in Part II must make written application to the Secretary's Office not later than April 15, 1946.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty, under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1947 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PAUL TITUS, M.D.

The following diplomates have been certified and are added to the previously published list: Dr. Frederick W. Bald, 1217 Union Industrial Building, Flint, Michigan; Dr. John P. Redgwick, 1530 Medical Arts Building, Omaha, Nebraska.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Edward A. Schumann, Philadelphia, Pa. *Secretary,* Howard C. Taylor, Jr. 842 Park Ave., New York, N. Y. Annual meeting Hershey, Penn., June 3-6, 1946.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* Lewis F. Smead, Toledo, Ohio. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1946.

Central Association of Obstetricians and Gynecologists. (1929) *President,* John H. Moore, Grand Forks, N. D. *Secretary-Treasurer,* W. F. Mengert, Dallas, Tex. Annual meeting Chicago, Ill., October, 1946.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* Robert A. Ross, Durham, S. C. *Secretary,* T. J. Williams, University, Va. Annual meeting on steamer, Tampa to Havana, Feb. 7-8, 1947.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Philip F. Williams, Philadelphia, Pa. *Secretary,* William Mengert, 2211 Oak Lawn Ave., Dallax Tex. Annual meeting San Francisco, July 1-7, 1946.

New York Obstetrical Society. (1863) *President,* R. A. Hurd. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* Bernard Mann. *Secretary,* John B. Montgomery, Pro tem, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* James E. Fitzgerald. *Secretary,* Herbert E. Schmitz, 25 East Washington Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* John J. Madden. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Carroll J. Fairo. *Secretary,* Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Charles Hunt. *Secretary-Treasurer,* Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* James S. Taylor. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* George Van S. Smith. *Secretary,* Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Roy J. Hefferman, Brookline, Mass. *Secretary,* Fred J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Goodrich C. Schauffer. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.

Washington Gynecological Society. (1933) *President,* James R. Costello. *Secretary,* Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* E. L. Zander. *Secretary,* R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. (1924) *President,* S. A. Weintraub. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary,* Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Robert B. Kennedy. *Secretary,* Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Obstetricians and Gynecologists. (1938) *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 E. Genesse St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Gerhard Ahnquist. *Secretary,* Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Roland S. Cron. *Secretary,* Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* R. C. Hall. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* A. L. Carson, Jr. *Secretary,* L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Sylvester Goodman. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held last Wednesday of each month.

Nassau Obstetrical Society. (1944) *President,* George B. Granger. *Secretary,* William S. C. Dolan, 2870 Northern Blvd., Manhasset, N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Harry Gordon. *Secretary-Treasurer,* J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* H. H. Skinner, Yakima. Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* J. Milton Singleton. *Secretary,* Richard C. Helman. Meetings, third Thursdays, September, November, January, March, and May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* George E. Judd. *Secretary,* Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Frank Locke, Winston-Salem. *Secretary,* Wallace B. Bradford, Charlotte, N. C. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* William A. Scott. *Secretary,* James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.